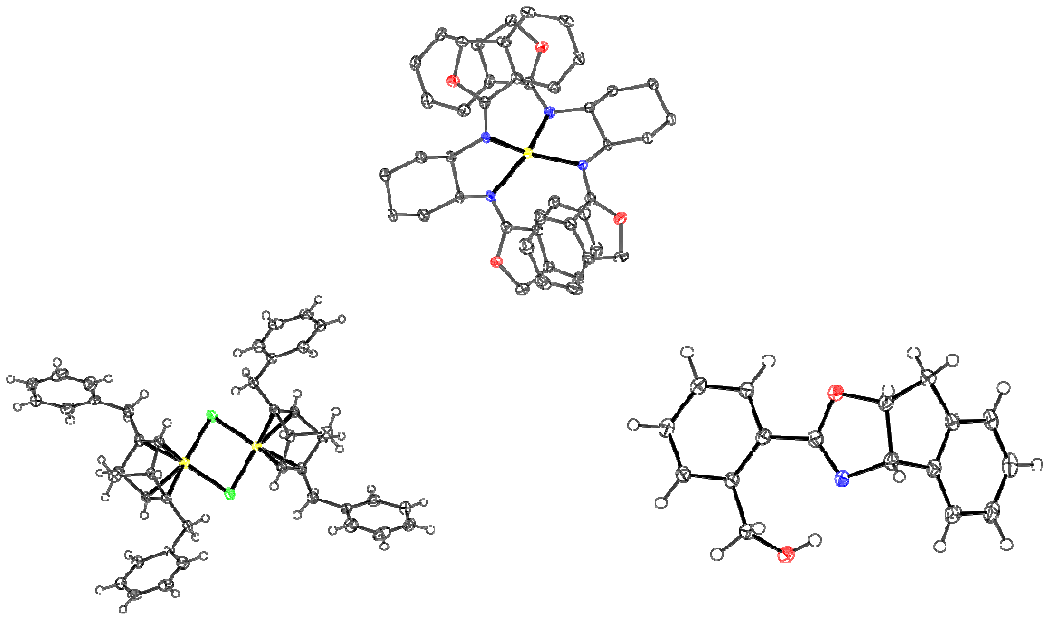
Faculty of Sciences

Department of Organic Chemistry

Laboratory for Organic and Bioorganic Synthesis

Synthesis and application of chiral dienes and chiral imidates as ligands for transition metal catalysis



Timothy Noël

Dissertation in order to obtain the degree of Doctor of Science: Chemistry.

Promoter: Prof. Dr. Johan Van der Eycken

-2009-

UNIVERSITEIT GENT

Faculty of Sciences

Department of Organic Chemistry

Laboratory for Organic and Bioorganic Synthesis

Synthesis and application of chiral dienes and chiral imidates as ligands for transition metal catalysis

Ph.D. dissertation in order to obtain the degree of Doctor of Science: Chemistry

by

Timothy Noël

Born 2 september 1982, Aalst.

Promoter: Prof. Dr. Johan Van der Eycken (Ghent University)

Reading Commission: Prof. Dr. Johan Van der Eycken (Ghent University)

Prof. Dr. Carsten Bolm (RWTH Aachen, Germany)

Prof. Dr. Erik Van der Eycken (K.U. Leuven)

Members of the Jury: Prof. Dr. Katrien Strubbe (Chairman, Ghent University)

Prof. Dr. Johan Van der Eycken (Ghent University)

Prof. Dr. Carsten Bolm (RWTH Aachen, Germany)

Prof. Dr. Erik Van der Eycken (K.U.L., Leuven)

Prof. Dr. Kourosch Abbaspour Tehrani (V.U.B., Brussel)

Prof. Dr. Pierre De Clercq (Ghent University)

Dr. Sam Verbrugghe (Ghent University)

CONTENTS

ACKNOWLEDGEMENTS

After four years of laboratory work, I am delighted to present in this thesis the results of my research. Completing a Ph.D. was really a dream come true, and it has been a privilege to be paid to do something I really enjoy.

A lot of people have contributed, in one way or another, to the writing of this thesis. It is, however, impossible to list all these names without forgetting one. Therefore, I apologize in advance.

First of all, I would like to thank my promoter Prof. Dr. Johan Van der Eycken who has given me the opportunity to prepare my Ph.D. in his laboratory. His continuous support and the freedom he gave to pursue my research has contributed significantly to the success of my Ph.D.

I would also like to acknowledge the support of Dr. Koen Vandyck, my supervisor in my predoctoral year. He gave me a lot of good advice, especially in the early stages of my Ph.D.

To Sam Verbrugghe I would like to express my gratitude for his continuous support throughout the patenting process. I am very grateful that I was given the opportunity to be so closely involved in this procedure. I learned a great deal from the experience.

A special word should also be directed to Engineer Jan Goeman, the handy-man of the S4 (a.k.a. the person who cannot say 'no'). Without his presence, I am convinced that none of the equipment of the S4 would work. Thanks for all LC-MS recordings, chiral recordings and all other practical help.

I would also like to thank my thesis students for their help with this work: Yilmaz Ozkilic, Elvan Er and Katrien Bert.

I also appreciate the help of Dr. Koen Robeyns and Prof. Dr. Luc Van Meervelt for the quick recording of the X-ray structures, the various X-ray figures (which I was unable to produce) and the interesting talks.

The recording of all the HRMS spectra was carried out by Stijn Claerhout and Prof. Dr. Erik Van der Eycken. I greatly appreciate their help in this.

Inside the S4, several assisting technical personnel should be acknowledged. For the NMR facilities I would like to thank the team of Prof. Dr. José Martins, consisting of Katrien, Tim, Roland and George. To Davy Sinnaeve as well, who helped me significantly (although he said it was nothing) with one chiral NMR experiment , I express my gratitude. I also thank Marc for the EI Mass spectra, Veerle for ordering the chemicals, Tom and Freddy for the help with several administrative problems, Dirk, Hector, Tom and Paul for replacing solvent barrels, etc.

I would like to show my sincere appreciation to Monica Sandor, Caroline Pieters and Merel Pieters for proof reading my publications and this manuscript.

Off course, I would like to thank the lab colleagues for the nice time I had in the S4: Jelle (my squash partner and roommate on several symposia), Frederique (a.k.a. The Marco and il piccolo grande), Yaşar and Zeki (for the nice dinners in the Sleepstraat), Ine, Pieter (for the talks about cycling), Sam (have you given back my 10 ml flask yet?), Rosa (your laugh is legendary), Karel-Simon, Katrien, Jurgen, Leen (for the willingness to listen), An, Vincent, Gert, Michel and Simon.

And last but certainly not least, I would like to thank my family and friends, especially my wife Merel and my parents. I cannot thank them enough for their continuous support in everything I do and the opportunities they gave me.

Thanks to all of you!

Timothy Noël
September 2009

ABBREVIATIONS

Acac	Acetylacetonate
Ac	Acetyl
APT	Attached Proton Test
APCI	Atmospheric Pressure Chemical Ionization
aq	Aqueous
Ar	Aryl
b	Backdonation
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-binaphthol
Bn	Benzyl
bp	Boiling point
BSA	N,O-bis-(trimethylsilyl)acetamide
c-	Cyclo-
℃	Temperature in degrees centigrade
CALB	Candida antarctica lipase B
CDA	Charge Decomposition Analysis
COD	1,5-cyclooctadiene
d	Donation
Dba	Dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DET	Diethyl tartrate
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DiPAMP	Ethylene((*o*-anisyl)phenylphosphine)
DIPEA	Diisopropylethylamine
DME	Dimethoxyethane
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	Bis-(diphenylphosphino)ferrocene
dvds	Divinyltetramethyldisiloxane
% ee	% Enantiomeric excess
E	Entgegen
EI	Electron Impact
ES	Electro Spray
Et	Ethyl
Et_2O	Diethylether
EtOAc	Ethylacetate
ETS	Extended Transition State
Equiv	Equivalents
FDA	Food and Drug Administration
GC	Gas Chromatography
h	Hour (hours)
HATR	Horizontal Attenuated Total Reflectance
hfc	3-(heptafluoropropyl-hydroxymethylene)-d-camphorate
HPLC	High Pressure Liquid Chromatography

HRMS	High Resolution Mass Spectroscopy
HSQC	Heteronuclear single quantum correlation spectroscopy
i-Bu	Isobutyl
IR	Infrared
J	Joule (= 0.2390 cal)
KHMDS	Potassium hexamethyldisilazide
L	Ligand
LC	Liquid Chromatography
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
M	Metal
Me	Methyl
MHz	Megahertz
MOP	2-(diphenylphosphino)-2'-methoxy-1,1'-binaphtyl
mp	Melting point
MS	Mass Spectroscopy
MTBE	Methyl Tertiary Butyl Ether
n.a.	Not applicable
nbd	Norbornadiene
NBS	*N*-bromosuccinimide
n-BuLi	*n*-Butyllithium ($CH_3CH_2CH_2CH_2Li$)
n.c.	No conversion
n.d.	Not determined
NHC	N-heterocyclic carbenes
NMR	Nuclear Magnetic Resonance
n.r.	No reaction
Ph	Phenyl
PhINTS	(*N*-(*p*-toluenesulfonyl)imino)phenyliodinane
ppm	Parts per million
R	rectus
rac	racemic
R_f	Ratio to front or retention factor
R.T.	Room temperature
S	sinister
Sat.	saturated
Sec-BuLi	*sec*-Butyllithium ($CH_3CHLiCH_2CH_3$)
SMB	Simulated Moving Bed
TADDOL	α, α, α', α'-tetraaryl-4,5-dimethoxy-1,3-dioxolane
t-Bu	Tertiary Butyl
Tf (OTf)	Triflate (trifluoromethylsulfonyl)
Tfb	tetrafluorobenzobarrelene
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMANO	Trimethylamine-N-oxide
TMS	Trimethylsilyl
TMEDA	N,N,N',N'-tetramethylethylenediamine
TON	Turn Over Number
TOF	Turn Over Frequency
Tris	2,4,6-triisopropylbenzenesulfonyl
Ts	Tosyl (*p*-toluenesulfonyl)

XRD	X-Ray Diffraction
Z	Zusammen
θ	Cone Angle

1

INTRODUCTION

1.1 CHIRALITY

"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized cannot be brought to coincide with itself."

Lord Kelvin, Baltimore Lectures.

The term "chiral" is used to describe an object that is non-superimposable on its mirror image. Lord Kelvin (William Thompson) introduced the term into science. The term "chirality" is derived from the Greek word for hand, χειρ (/cheir/). Our hands are indeed an excellent macroscopic example of chirality. The two mirror images are called enantiomers.

Examples of macroscopic chirality can be found all around us, from medieval spiral stairwells, right- or left-handed screws and propellers, the left-right asymmetry of internal organs with humans[1], chiral snail shells[2] to chiral bacterial-colony formation[3] (Figure 1.1).

Figure 1.1. *Examples of macroscopic chirality, from left to right: (a) spiral stairwells, (b) chiral snail shells, (c) chiral bacterial-colony formation.*

In sharp contrast with this macroscopical chirality, which is easy to observe, the discovery of molecular chirality lasted till the 19th century. The French physicist Biot

established that certain organic compounds rotated the plane of polarization of light. However, it was Pasteur who correlated this phenomenon with an asymmetric grouping of atoms within molecules. He investigated solutions of sodium ammonium tartrate which did not rotate the plane of polarized light. After crystallization of the solutes, he noticed that the crystals came out in two asymmetric forms. Sorting both forms by hand, he discovered that one form rotated polarized light clockwise while the other form rotated light counterclockwise. Kekulé found that carbon should have four valences. This finding together with the finding by van't Hoff and Le Bel that these valences should be arranged in a tetrahedral fashion set the stage for the possibility of organic molecules to exist in mirror-image forms or enantiomers.

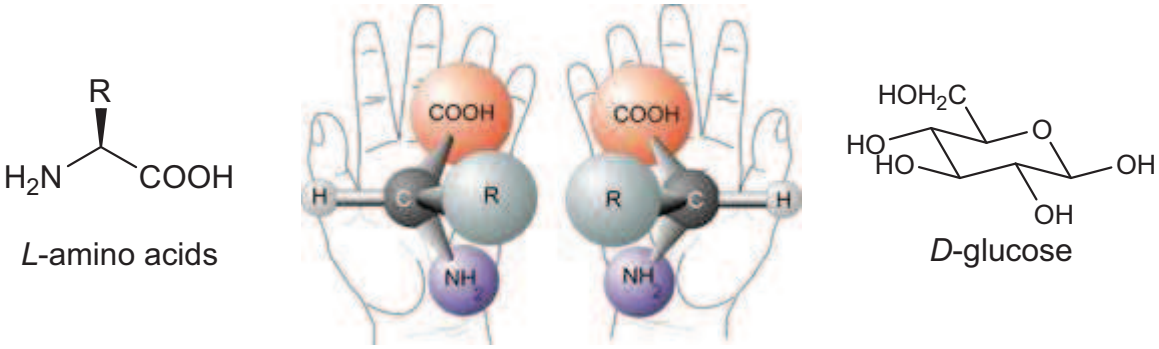


Figure 1.2. *Molecules in two mirror-image forms and chiral biologically active molecules.*

Chiral molecules are present in the most fundamental processes of life. The sugars that constitute DNA and RNA possess a uniform stereochemical configuration. The proteins, encoded by these oligonucleotides, consist of chiral *L*-amino acids. Homochirality, reflecting the fact that biomolecules are built from chiral building blocks, is generally recognized as a fundamental property of life. The origin of this homochirality is, in spite of numerous theories, still unclear.[4] Nature has in some cases taken advantage of its own homochirality through the use of post-translational reactions to convert *L*-amino acids into the corresponding *D*-enantiomers. The resulting peptides and proteins exhibit an enhanced stability towards enzymatic degradation.[5]

Since chirality is an integral part of all biological processes, enantiomers may differ both quantitatively and qualitatively in their biological activities.[6] At one extreme, one enantiomer may be devoid of any biological activity; at the other extreme, both enantiomers may have qualitatively different biological activities. These stereoselective differences may arise not only from drug interactions at pharmacological receptors but also from pharmacokinetic events.[7] This can express itself in a different taste[8], smell, toxicity or therapeutic effect (Figure 1.3). The thalidomide tragedy of 1961 is one of the most famous examples where the two enantiomers have a totally different biological activity. Thalidomide was prescribed as a racemate for pregnant women as an antiemetic against morning sickness. Whereas the (*R*)-enantiomer had the desired activity, the (*S*)-enantiomer proved to be teratogenic. However, the tragedy could not have been avoided if only a single enantiomer would have been used and that for two reasons. Firstly, studies in rabbits showed that both enantiomers show equal teratogenic potency.[9] Secondly, the chiral centre in thalidomide is unstable in acidic media and undergoes a rapid

racemization.[10] But, this tragic example resulted in an increasing awareness of the stereoselectivity of drug action. In addition, since 1992 the Food and Drug Administration (FDA) policy states that in the development of a drug with a stereogenic center, both enantiomers should be evaluated *in vivo* at an early stage.[11]

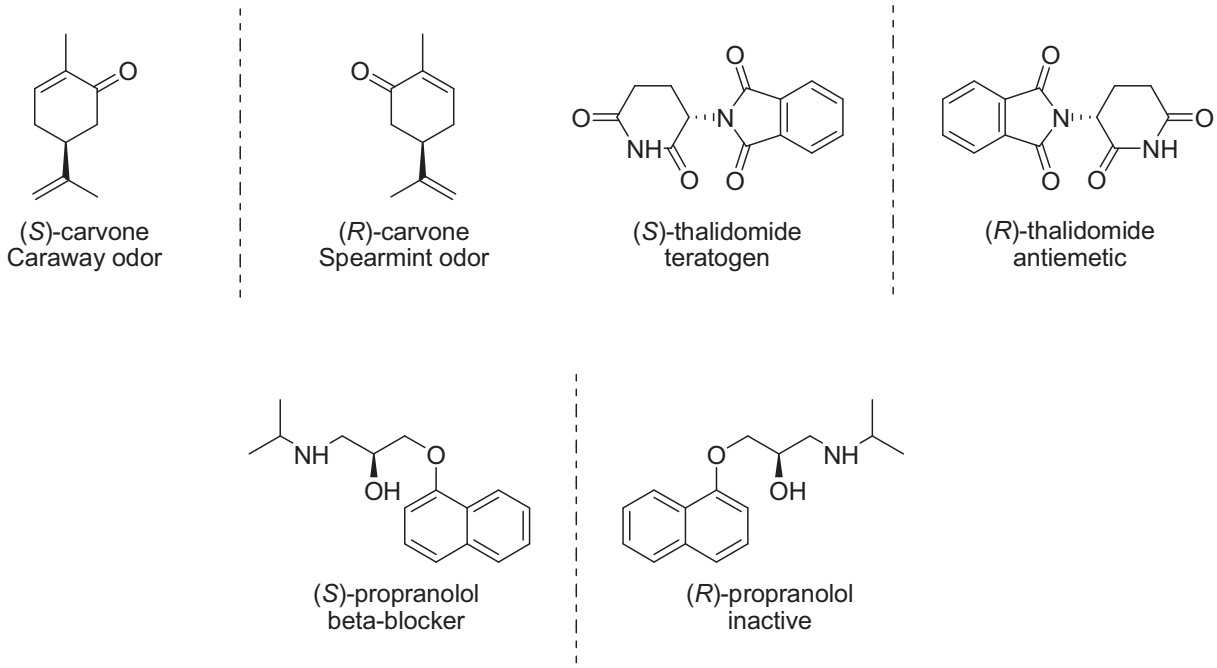


Figure 1.3. *The different activities of enantiomers.*

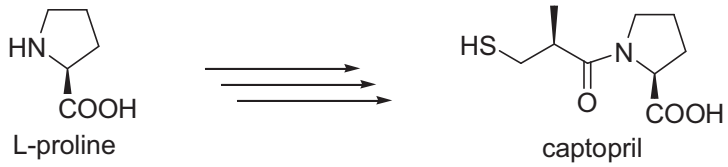
Till the mid-1950s, it was generally believed that all four fundamental forces of nature were perfectly symmetrical.[12] At that time, there existed the so-called "thau-theta puzzle". These two particles decayed differently while they should have similarly. This could only be explained under the assumption that one of their fundamental properties was not the same. In 1956, Yang and Lee published a paper where they considered that parity might be violated and that there could be an asymmetry in nuclear β-decay.[13] In this paper, several experiments were proposed to check whether parity is conserved in the weak interactions or not. One of these experiments involved the measurement of the β-decay of cobalt-60 atoms. A few months later, it was shown that cobalt-60 nuclei, spinning in the same direction around the z-axis, underwent β-decay and emitted more electrons in the –z direction than in the +z direction.[14] This result is not invariant under a mirror reflection, indicating that the interaction responsible for the decay process, i.e. the weak interaction, does not conserve parity. After the parity violation was proven, also charge-parity violation (CP violation) was discovered.[15] But, when time-reversal (T) is considered, it is still believed that CPT-symmetry is conserved.

Parity violation leads to an energy difference between two enantiomers in the 10^{-12}-10^{-15} J/mol range. These subtle energy differences can, however, not explain the origin of homochirality in nature.[16]

1.2 ASYMMETRIC SYNTHESIS

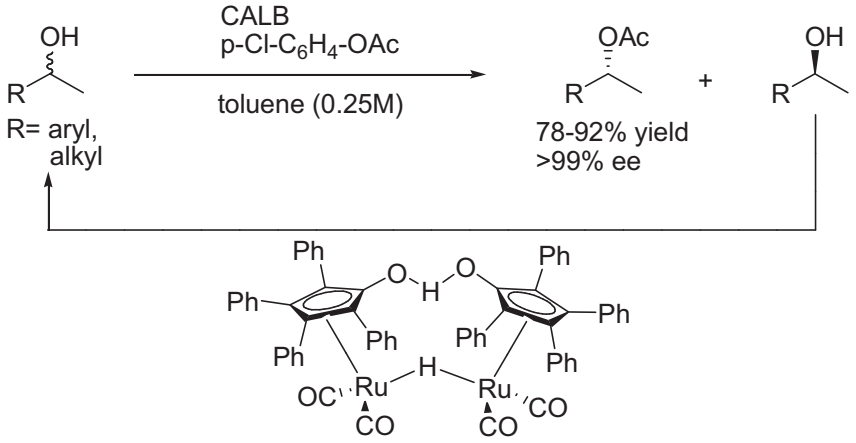
A large amount of the pharmaceuticals and agrochemicals contain one or more stereogenic centers. Several possible approaches have been developed to access these enantioenriched compounds.

A first possibility is the so-called chiral pool approach which starts from readily available chiral building blocks originated from nature, e.g. sugars, amino acids, terpenes, hydroxyacids and alkaloids. This method is commonly used in early phases of drug synthesis. Given the homochirality of nature, the opposite enantiomer is often difficult to obtain. An example is given in scheme 1.1, the synthesis of captopril, an ACE inhibitor, starts from L-proline.



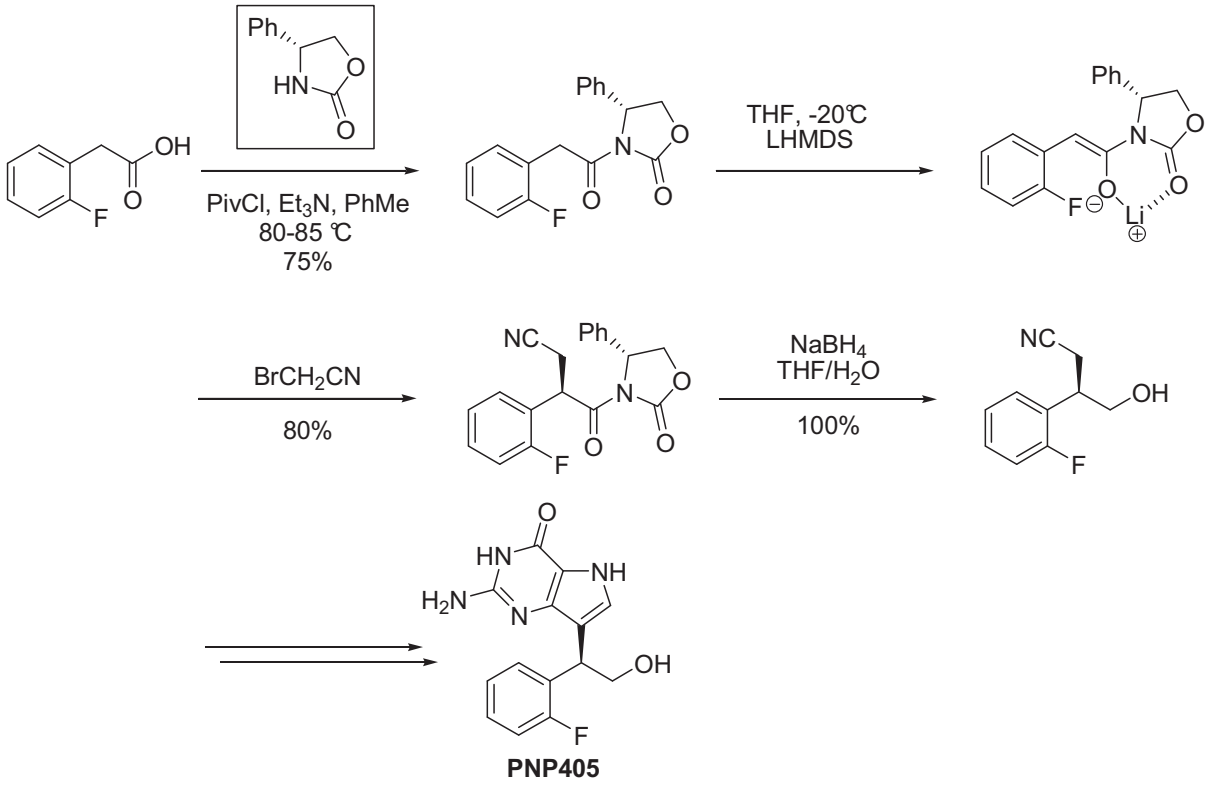
Scheme 1.1. *Synthesis of captopril starting from (L)-proline.*

A second possibility is the separation of the two enantiomers by means of a resolution step. This can be done via a classical resolution, i.e. a crystallization of diastereomeric adducts. Recently, a new and intriguing technique for obtaining a single enantiomer was reported.[17] Solution-solid mixtures with a composition of 2-3% ee were magnetically stirred in the presence of glass beads. A soluble racemizator was added to this mixture. It appeared that the ee of the solid raised in function of the time until a solid of single chirality was obtained. This shows that a slight imbalance in enantioselectivity can lead to a single solid chiral state. Another possibility to separate two enantiomers is via chiral HPLC, where the enantiomers are separated over chiral stationary phase columns.[18] Using simulated moving bed techniques (SMB), the chiral separation can be done continuously on an industrial scale.[19] Although 50% of the material is the wrong enantiomer, resolution is still the most commonly used technique in industrial asymmetric syntheses.
An interesting technique is a kinetic resolution. The two enantiomers show different reaction rates in a chemical reaction and if the difference is large enough, in theory, only one of the two is converted. An important extension is the dynamic kinetic resolution. Hereby the unwanted enantiomer racemizes *in situ* while the other enantiomer is constantly reacting away. Hence, conversions of 100% are theoretically possible. An interesting example of a dynamic kinetic resolution, where a biocatalyst (CALB) is combined with a metal racemisation catalyst, is shown in scheme 1.2.[20]



Scheme 1.2. *Dynamic kinetic resolution of secondary alcohols with a ruthenium racemisation-catalyst*

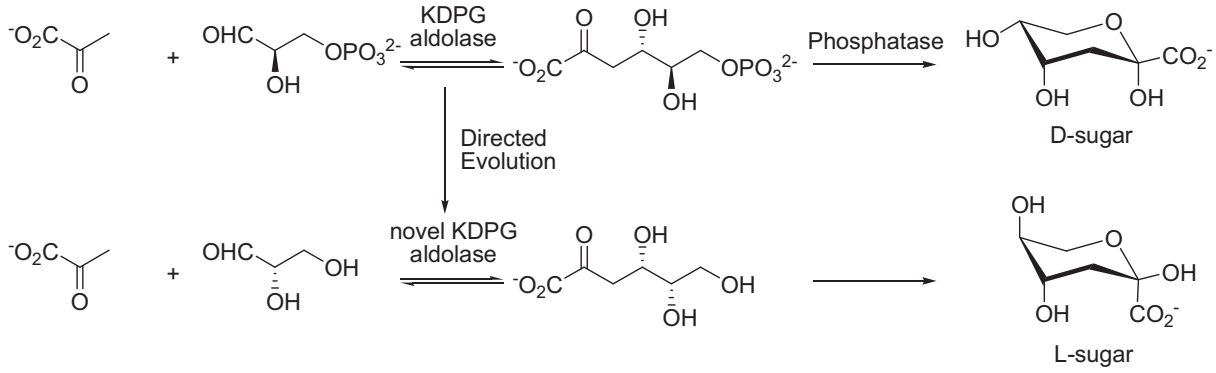
Another approach involves the use of chiral auxiliaries. In this strategy the prochiral substrate is attached to a chiral, non-racemic group, known as the chiral auxiliary, prior to reaction. The two possible products then become diastereoisomeric and thus only one could be formed in excess. Although the reactions are highly predictable and reliable, this method requires additional reaction and purification steps, and stoichiometric amounts of chiral auxiliary are necessary (Scheme 1.3).



Scheme 1.3. *Synthesis of PNP405 with (R)-4-phenyl-2-oxazolidinone as a chiral auxiliary.*

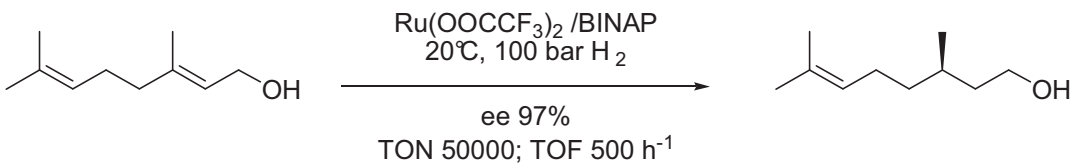
However, the best way to introduce chirality is to use a chiral catalyst because only a small amount of highly valuable catalyst is required to obtain a large amount of chiral target product. There are three fundamentally different approaches to obtain enantiomerically pure compounds via catalysis.

A first approach is biocatalysis. Nature uses chiral, non-racemic catalysts (enzymes) to carry out many enantioselective reactions. Although the induced enantioselectivity is often impressive, these biocatalysts have a very high substrate-specificity and their use in organic solvents is rather difficult. A notorious exception to this rule are hydrolases, like lipases and esterases. These problems can be partly overcome thanks to the tremendous advances recently made in the field of biocatalysis. This is due to the apparition of novel techniques such as directed evolution[21], the use of enzymes in organic solvents[22], etc. (Scheme 1.4).



Scheme 1.4. *Access to both enantiomers of a sugar via enzymatic catalysis.*

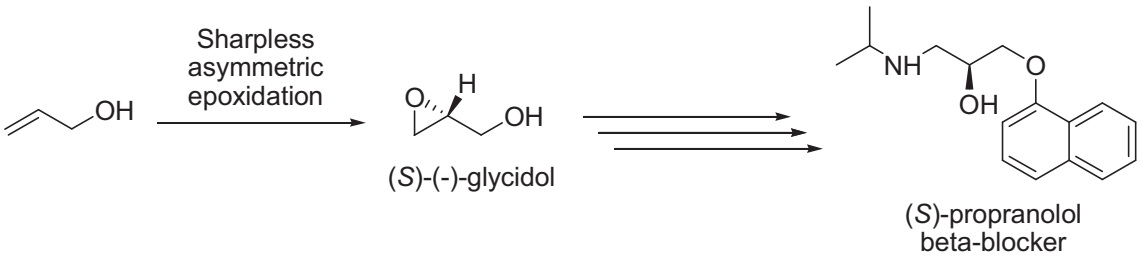
A second approach is the use of transition metal complexes. These complexes consist of a chiral organic ligand bound to a transition metal. The chiral ligand modifies the reactivity and selectivity of the metal center in such a way that only one of the two possible enantiomers is preferentially formed. The wide variety of chiral organic ligands that can be combined with several transition metals, makes this method the most versatile to use in asymmetric syntheses. An example of an industrial process with a chiral transition metal complex can be found in scheme 1.5.[23]



Scheme 1.5. *Industrial synthesis of citronellol by Takasago.*

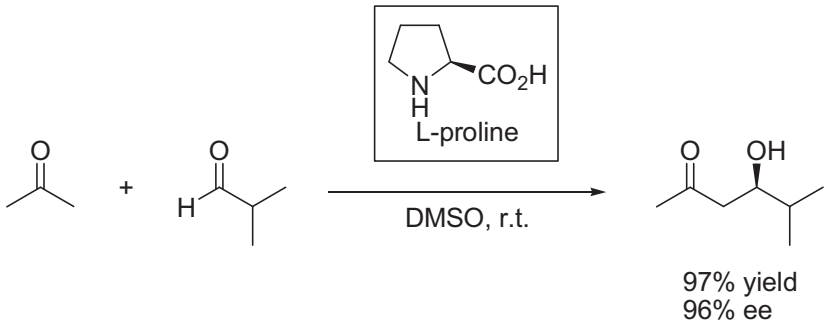
Given the success of several asymmetric transition metal-catalyzed processes, e.g. the Sharpless asymmetric epoxidation, synthetic chemists can now devise strategies to prepare target structures based on chiral starting materials which are unavailable from nature. These unnatural starting materials are new cheap sources of enantiomerically pure products and they fulfill the same role as the products from the 'natural' chiral pool. Therefore it was suggested to consider these products as

members of a 'new' chiral pool.[24,25] An example is given in scheme 1.6, glycidol is synthesized via a Sharpless asymmetric epoxidation. This member of the 'new' chiral pool was used in the synthesis of (*S*)-propranolol.[26]



Scheme 1.6. *Synthesis of (S)-propranolol starting from (S)-(-)-glycidol.*

Between the extremes of transition metal catalysis and biocatalysis, a third approach to the catalytic production of chiral compounds has emerged, i.e. organocatalysis.[27,28,29] In sharp contrast with transition metal catalysis, the organic molecule itself functions as the catalyst. Proline, a chiral pool compound, is a classical example of an organocatalyst. It catalyzes aldol and related reactions by iminium or enamine pathways (Scheme 1.7).[30]



Scheme 1.7. *Proline-catalyzed intermolecular aldol reaction.*

1.3 THE DEVELOPMENT OF ENANTIOSELECTIVE TRANSITION METAL CATALYSIS[31]

The principle of asymmetric catalysis is illustrated in figure 1.4.[32,33] The initially used chiral precatalyst is activated into a catalyst via an induction process. This catalyst consists of a metal or a metal ion and a chiral organic ligand. The ligand stabilizes the metal and creates a chiral environment. The catalyst activates prochiral molecules A and B and reversibly forms an intermediate. The chiral environment around the metal is the origin of the chiral induction and, therefore, a chiral product AB is formed and the catalyst is regenerated.

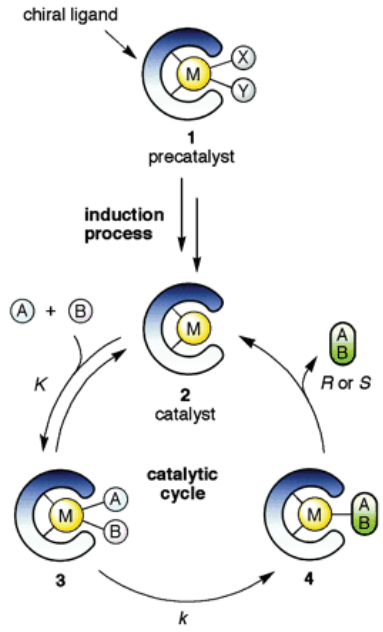
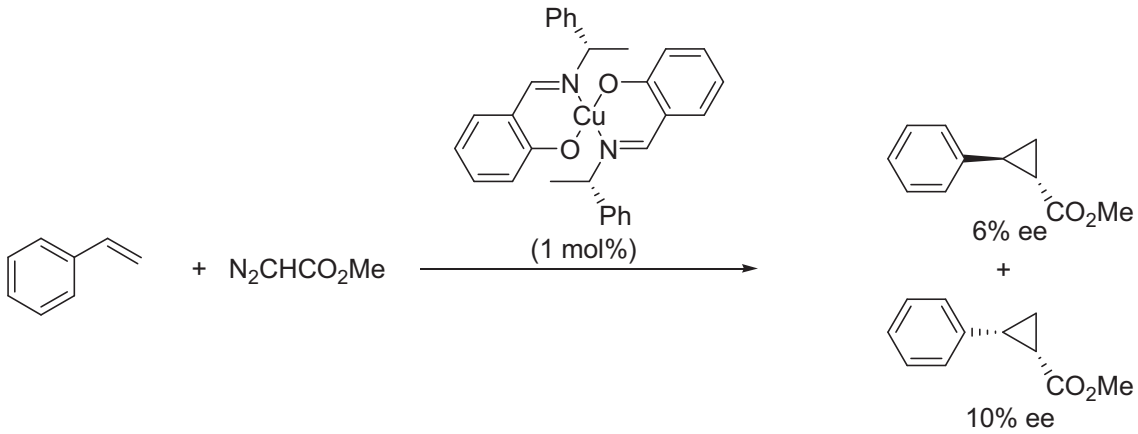


Figure 1.4. *The principle of asymmetric catalysis with chiral organometallic molecular catalysts.*

The first example of homogeneous asymmetric catalysis was performed by Natta in the polymerization of benzofuran with an $AlCl_3$-phenylalanine catalyst. Optical activity was detected for the polymer. However, it is difficult to estimate the efficiency of the chiral induction process from an optical rotation of a polymer.[34]

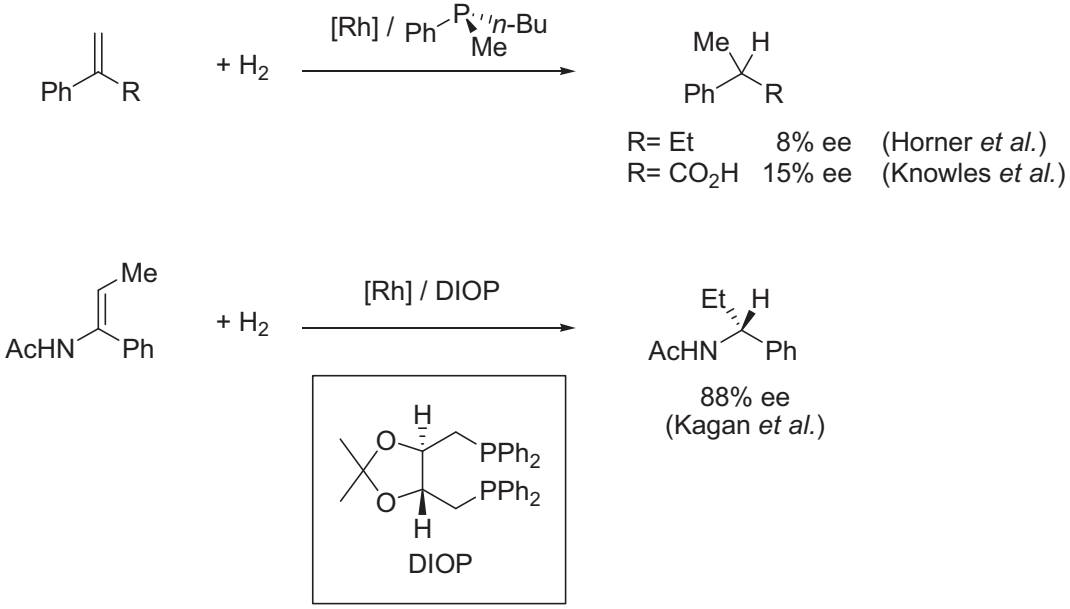
The first example of asymmetric organometallic catalysis outside the field of polymer chemistry was the cyclopropanation of alkenes by Nozaki and Noyori in 1966.[35] A chiral salen-copper catalyst gave selectivities up to 10% ee (Scheme 1.8). Although the selectivity was low, this result was a significant achievement and initiated further research in asymmetric catalysis.



Scheme 1.8. *Cu-catalyzed asymmetric cyclopropanation.*

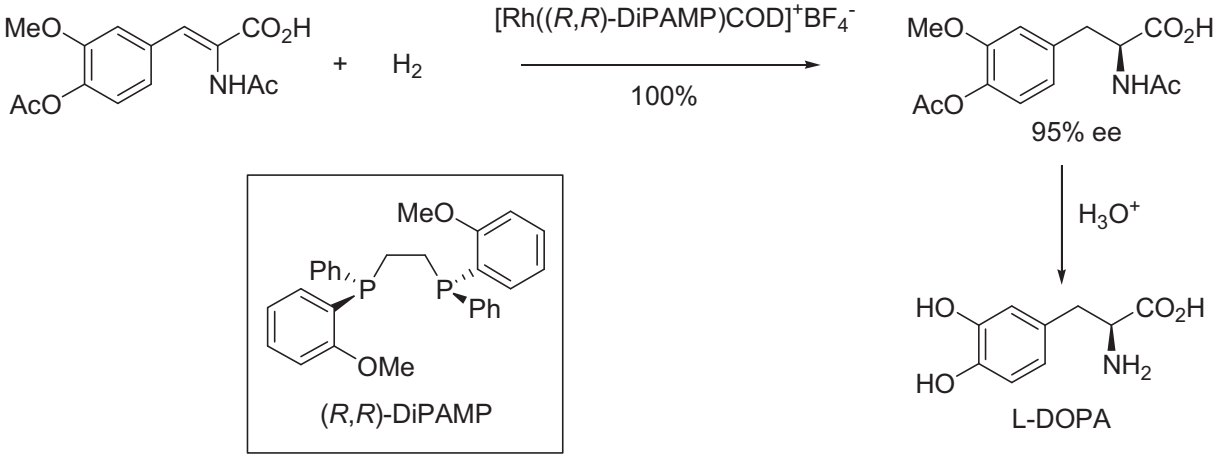
In that same year, Wilkinson performed the first homogeneous catalytic hydrogenation reaction with $RhCl(PPh_3)_3$ as a catalyst.[36] Stimulated by this finding, Horner *et al.*[37] and Knowles *et al.*[38] found, independently from one another, that the

use of a chiral phosphane ligand in the rhodium-catalyzed hydrogenation induced modest enantioselectivities into a prochiral alkene. In 1971, Kagan *et al.* synthesized the first C_2-symmetrical diphosphane ligand, named DIOP.[39] The idea behind this was that a C_2-symmetrical ligand would lead to a better defined transition state complex with, hopefully, a beneficial effect on the induced enantioselectivity. Enantioselectivities up to 88% ee were obtained with DIOP in the hydrogenation of enamides.



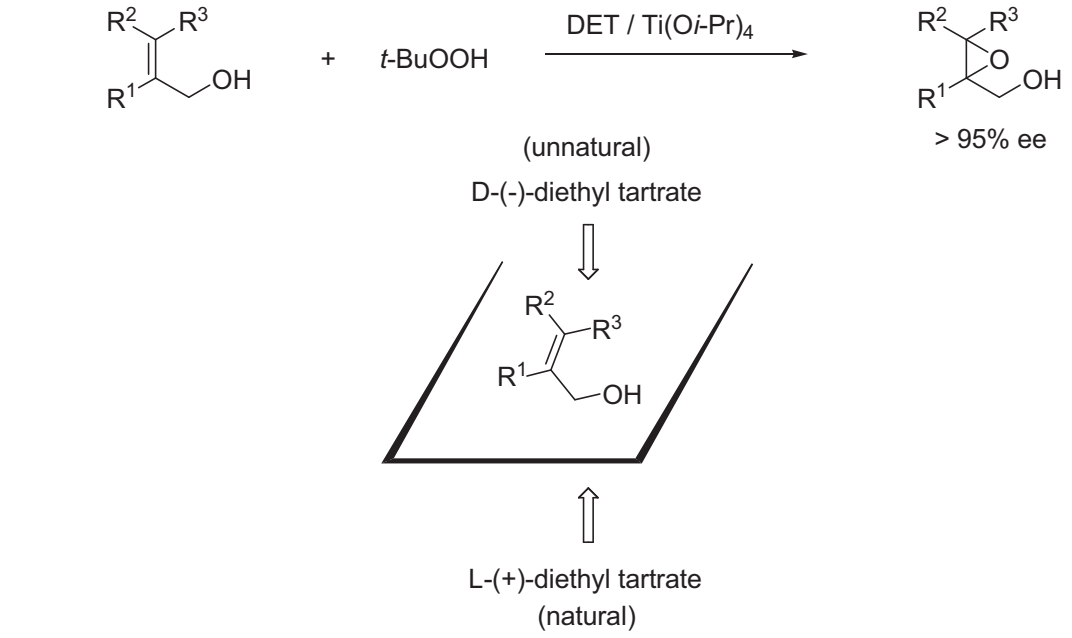
Scheme 1.9. *Pioneering work in the rhodium-catalyzed asymmetric hydrogenation.*

Inspired by the work of Kagan *et al.*, Knowles *et al.* developed the C_2-symmetrical DiPAMP.[40] This diphoshane ligand combines the good chelating properties of a bidentate C_2-symmetrical ligand and the good chirality inducing properties of a chiral phosphorous atom. This ligand was used in the asymmetric synthesis of L-DOPA at Monsanto and was the first example of an industrial asymmetric synthesis (Scheme 1.10).

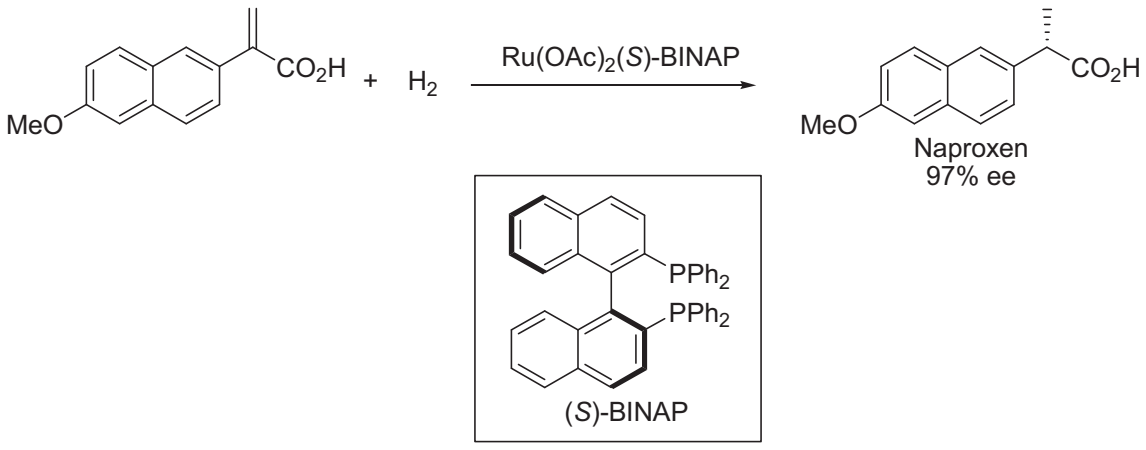


Scheme 1.10. *The Monsanto synthesis of L-DOPA using a catalytic asymmetric hydrogenation.*

In 1980, two significant breakthroughs in the field of asymmetric catalysis were published. The first one was the asymmetric epoxidation of allylic alcohols by Sharpless and Katsuki.[41] This method allowed a great deal of flexibility within the structure of the substrate. However, there is one restriction: the presence of an allylic alcohol is necessary (Scheme 1.11). The second breakthrough was the preparation of BINAP by Noyori *et al.*[42] This C_2-symmetrical diphosphane is characterized by a full aromatic substitution and is known to have superior chirality recognition and induction abilities.[43] Through the years BINAP has become one of the most versatile ligands known in asymmetric catalysis. E.g., BINAP is used as a ligand in the synthesis of naproxen, an analgesic and anti-inflammatory agent (Scheme 1.12).[44]



Scheme 1.11. *Sharpless asymmetric epoxidation of allylic alcohols.*



Scheme 1.12. *Synthesis of naproxen via a ruthenium/BINAP-catalyzed asymmetric hydrogenation.*

Since then, the number of significant results in the field of asymmetric synthesis has grown exponentially. The most important are: the Sharpless asymmetric dihydroxylation[45], the Jacobsen asymmetric epoxidation[46], the synthesis of the DUPHOS ligand family[47], synthesis of oxazoline ligands[48], the asymmetric allylic substitution[49], etc.

In 2001, K.B. Sharpless, W.S. Knowles and R. Noyori received the Noble Prize in Chemistry for their contributions to the development of catalytic asymmetric synthesis.[50]

1.4 CHIRAL ORGANIC LIGANDS FOR ASYMMETRIC TRANSITION METAL CATALYSIS

The choice of an appropriate ligand is crucial for the success of an asymmetric transition metal-catalyzed reaction. Given the complexity of most catalytic processes, a rational design of a chiral ligand is seldom straightforward. Therefore, the synthesis of new ligands is often the result of a knowledge-based intuition or serendipity.

A chiral ligand has to fulfill a list of demands to be attractive to the organic chemist. Several important requirements can be distinguished[51,52] (Table 1.1).

Requirements for chiral ligands
1. Wide scope (with well defined and known limitations);
2. Air and/or moisture stable;
3. Modular, straightforward and easily up-scalable synthesis;
4. High chemoselectivity;
5. Catalyst performance: high enantioselectivity, high TON, high TOF;
6. Freedom to operate: patent protection and licensing;
7. Marketing;
8. Speed to implement the process and process robustness.

Table 1.1. *Ligand success factors.*

Certain classes of ligands are enantioselective over a wide range of different reactions. These ligands are called 'privileged chiral ligands'.[53,54] In figure 1.5, a few important privileged ligands and catalysts are shown, e.g. BINAP[43], MeDUPHOS[55], cinchona alkaloids[56], Brintzinger's ligand[57], TADDOL[58], MonoPhos[59], bisoxazolines[60], salen ligands[61] and Josiphos[62]. Most privileged ligands are C_2-symmetrical, possess a rigid structure and are bidentate ligands. However, these factors are not a prerequisite for a successful ligand structure.[63]

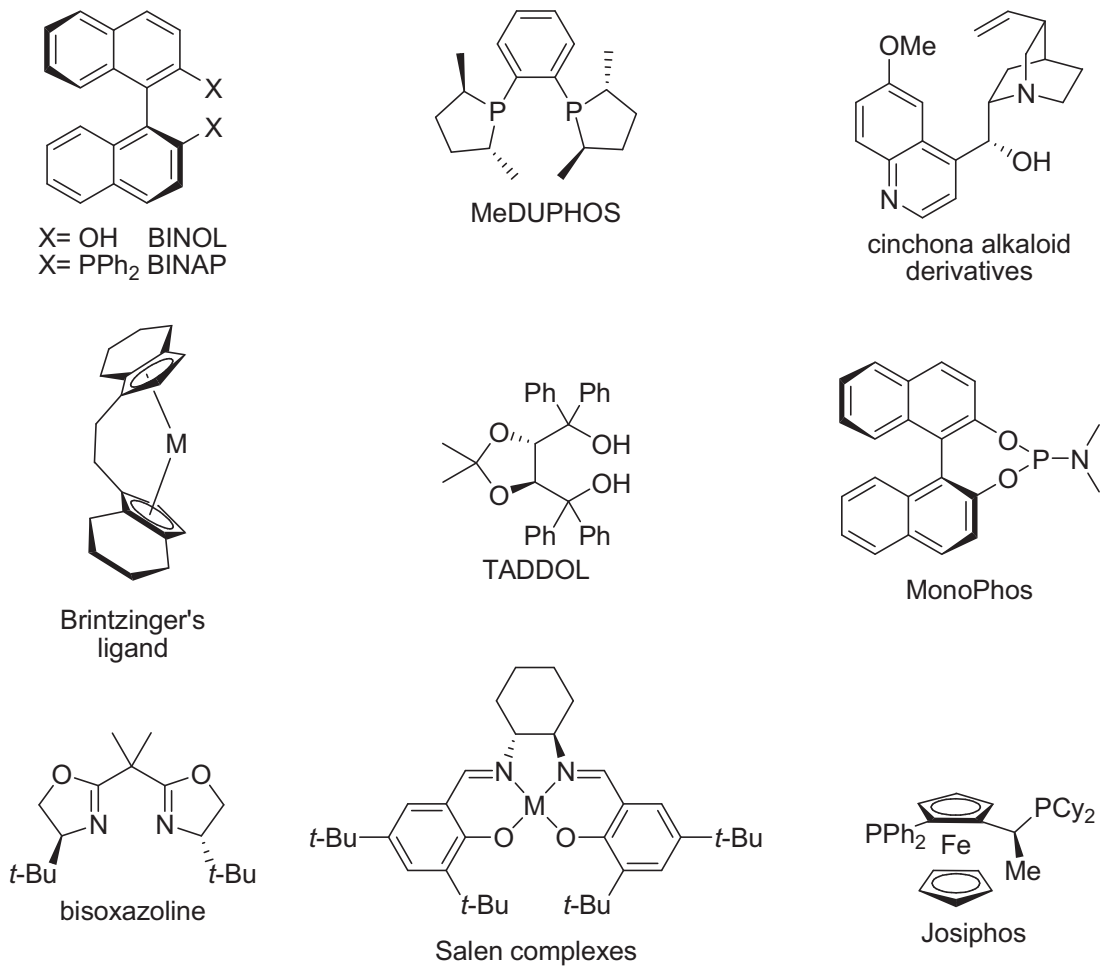
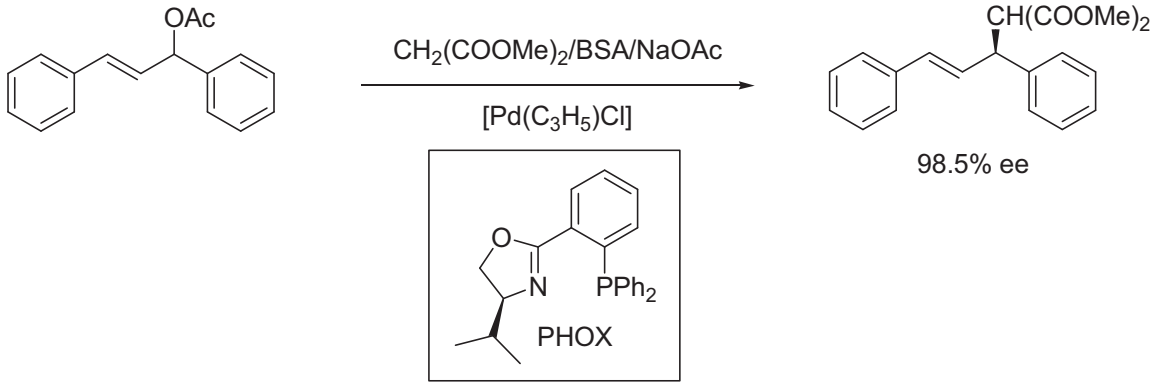


Figure 1.5. *Examples of privileged chiral ligands and catalysts.*

The presence of a C_2-symmetrical axis in a catalyst can reduce the number of possible competing diastereomeric transition states.[64] This can have a beneficial effect on the enantioselectivity because of the possible elimination of less-selective pathways. The C_2-symmetry is especially useful in mechanistic studies. However, there is no fundamental reason why a C_2-symmetrical ligand should be superior to a C_1-symmetrical ligand.[65] In some cases, a C_1-symmetrical ligand can give better enantioselectivities than the corresponding C_2-symmetrical ligand.[66] An interesting example is the synthesis of mixed P,N-ligands where the phosphorous atom is soft and the nitrogen atom is hard. This understanding led to the synthesis of so-called PHOX ligands (Scheme 1.13).[67] These ligands are highly successful in the asymmetric allylic alkylation reactions. Complexation of these ligands results in an electronic differentiation of the two allylic termini due to the higher *trans*-effect of phosphorous as compared to nitrogen. This results in an attack of the nucleophile *trans* to P.



Scheme 1.13. *Asymmetric allylic alkylation reactions with chiral PHOX ligands.*

The use of a ligand can be severely hampered if it is extremely air- and moisture sensitive. Since most catalysts are rather substrate specific, a modular structure of the ligand is advisable. As a result, the ligand can be tailored to the specific needs of each substrate class. A straightforward synthesis of the ligand class is an important advantage for its commercialization. Ligands have often complex structures or require special precautions while synthesizing or handling them, e.g. oxygen free conditions. If special precautions are not required, the ligand will be more readily used.

An easy synthesis is also a prerequisite for a ligand to be used on an industrial scale because it makes a fast implementation possible. The use of a ligand in an industrial process will also increase its availability on the market.

A catalyst should meet the high requirements that are demanded by the organic chemists. A high chemoselectivity is needed. In other words, the necessity of functional group protection should be kept as low as possible. The induced enantioselectivity should be high and predictable. To be commercially viable, the most important factor is the catalyst productivity, quantified as TON-[68] and TOF-numbers[69].

Most of the new and interesting ligands are patented both by academics and companies. However, a patented ligand is much less likely used by chemists in the industry because of uncertainties regarding the freedom to operate and the royalty costs.

Marketing is a very important factor in the development of a catalyst. Nowadays, the synthesis of new ligands grows exponentially, meaning that the choice is overwhelming. A good promotion strategy consists of writing publications and reviews, giving lectures, etc. This is necessary to persuade the chemical community of the utility of a new ligand design.

A catalytic step must be easily implemented in the, sometimes, existing industrial process. The earlier in the process an asymmetric catalytic step can be implemented, the greater the chance it will be applied on a commercial scale. Moreover, scaling up of a catalytic step from laboratory scale to production scale must be predictable. The catalytic step should be able to work reliable even when there are small variations in the process, which are typical for production operations.

1.5 ASYMMETRIC SYNTHESIS ON AN INDUSTRIAL SCALE

In recent years, there has been a movement away from racemic compounds towards the production of enantiomerically pure compounds (Table 1.2).[70] This trend is caused by the stricter regulations of regulatory authorities worldwide. Since 1992, the FDA demands that for every newly designed chiral drug a systematic characterization of each enantiomer is performed. In addition, the possibility of an extension of a patent term, by means of a so-called 'chiral switch', resulted in an increasing interest in asymmetric synthesis.[71] 'Chiral switches' are chiral drugs that have already been claimed, approved and marketed as racemates or as a mixture of diastereoisomers, but have been redeveloped and 'repatented' as single enantiomers. However, the prerequisite for patentability is that the two enantiomers of a chiral drug should display sufficiently different pharmacological effects from both each other and the racemate.

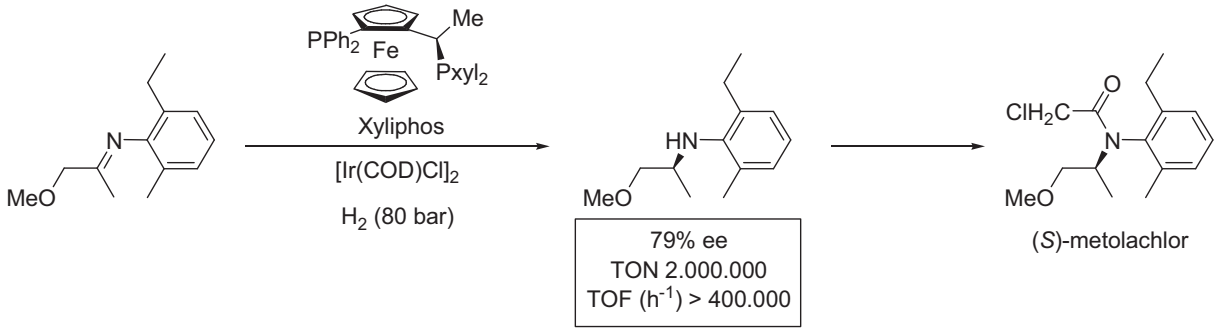
Year	Racemates[a]		Single Enantiomers		Achiral	
	Worldwide (%)	FDA[b] (%)	Worldwide (%)	FDA[b] (%)	Worldwide (%)	FDA[b] (%)
1983	37	n.a.	26	n.a.	37	n.a.
1984	28	n.a.	26	n.a.	46	n.a.
1985	38	n.a.	22	n.a.	40	n.a.
1986	26	n.a.	26	n.a.	48	n.a.
1987	18	n.a.	49	n.a.	33	n.a.
1988	26	n.a.	39	n.a.	35	n.a.
1989	29	n.a.	26	n.a.	45	n.a.
1990	33	n.a.	35	n.a.	32	n.a.
1991	20	9	40	65	40	26
1992	21	33	44	42	35	25
1993	16	17	45	29	39	54
1994	38	5	38	57	24	38
1995	21	37	46	30	33	33
1996	9	14	41	43	50	43
1997	24	8	30	38	46	54
1998	15	9	50	41	35	50
1999	13	4	52	46	35	50
2000	9	19	62	37	29	44
2001	0	0	68	60	32	40
2002	6	0	55	53	39	47

[a] Including diastereomeric mixtures.
[b] n.a.: not applicable.

Table 1.2. *Annual distribution of worldwide and FDA-approved drugs according to their enantiomeric purity.*[72]

The same trend is also visible in the agrochemical industry. Use of only the active enantiomer, instead of the racemate, leads to reduced quantities and so to a reduced environmental impact. One of the best known examples of asymmetric catalysis on an industrial scale is the synthesis of (*S*)-metolachlor, a widely used herbicide

(Scheme 1.14).[73] For industrial asymmetric catalytic processes, the activity of the catalyst is the most important parameter. Xyliphos gave a lower but acceptable enantioselectivity (79% ee), however, the turnover number (TON) and turnover frequency (TOF) were very high.

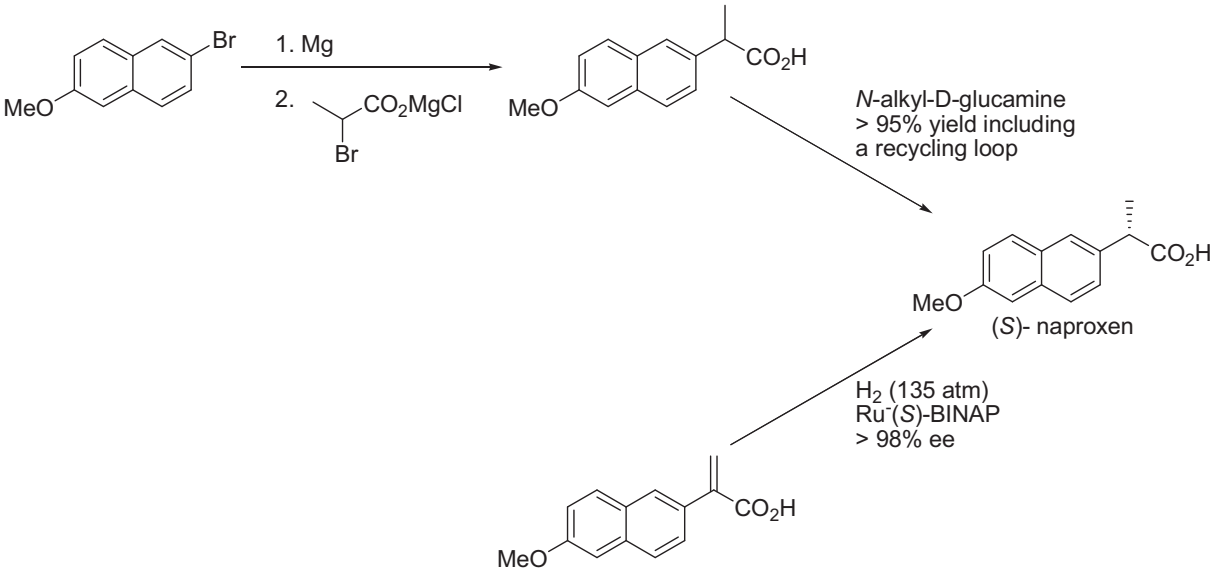


Scheme 1.14. *Industrial production of (S)-metolachlor.*

Two questions are important for deciding whether an asymmetric industrial process is appropriate in a certain case. Firstly, are the overall cost-of-goods in favor of an asymmetric synthesis or is the synthesis of a racemate with a resolution afterwards economically more favorable? Secondly, what is the chance that the development of a reliable asymmetric step will be successful?[74,75]

In industry, alternatives for asymmetric syntheses, e.g. resolutions and using chiral pool products as starting materials, are still more popular. There are two main reasons for this.
Firstly, asymmetric syntheses are considered as complicated and sensitive to small changes in the reaction conditions. Conversely, resolutions of racemic mixtures are pretty straightforward. As soon as the ideal resolving agent has been identified, the rest of the process is relatively easy. In other words, the implementation in an existing process can be faster done for a resolution than for asymmetric methodologies.
Secondly, given the fact that in the pharmaceutical industry 90% of the selected drug candidates are discontinued before they reach the market, designing a time-consuming asymmetric synthesis can be too expensive. The use of a resolution step is far more attractive because it allows a rapid delivery of the target product at a large scale.

An example where the classical diastereomer resolution with an *in situ* racemization step is preferred over the enantioselective syntheses, is the synthesis of (*S*)-naproxen, a non-steroidal anti-inflammatory drug (NSAID) (Scheme 1.15).[76] There are several reasons for this. Firstly, the resolution process with a racemization-recycling loop is almost perfect (>98% yield). Secondly, the starting reagents are much cheaper for the resolution than for the asymmetric catalytic syntheses. And finally, the enantioselective catalytic transformation is not perfect (98% ee), as a result an additional recrystallization step is required to obtain the enantiomerically pure product.



Scheme 1.15. *Side-by-side comparison of two possible approaches towards the synthesis of (S)-naproxen.*

But, syntheses that produce racemates suffer from several drawbacks. Half of the material will be lost or has to be recycled. In times of an increasing environmental awareness, an important disadvantage is the use of large amounts of solvents and the production of other chemical waste. On the basis of this reasoning, industrial-scale synthesis of enantiomerically pure molecules can only be considered as 'green chemistry' when asymmetric catalytic methodologies are used. Tremendous advances over the recent decades have been made in asymmetric catalytic chemistry. Research in this field is still on the move. The popularity of the alternatives results from the generally perceived complexity of asymmetric catalysis. Nonetheless, convincing results will continue to accumulate and will drive this fascinating technology forward.

1.6 REFERENCES

[1] (a) Tubbs, R.S.; Wellons III, J.C.; Salter, G.; Blount, J.P.; Oakes, W.J. *Anat. Embryol.* **2003**, *206*, 199-202. (b) Ryan, A.K.; Blumberg, B.; Rodriguez-Esteban, C.; Yonei-Tamura, S.; Tamura, K.; Tsukui, T.; de la Pena, J.; Sabbagh, W.; Greenwald, J.; Choe, S.; Norris, D.P.; Robertson, E.J.; Evans, R.M.; Rosenfeld, M.G.; Belmonte, J.C.I. *Nature* **1998**, *394*, 545-551.

[2] Schilthuizen, M.; Davison, A. *Naturwissenschaften* **2005**, *92*, 504-515.

[3] Ben-Jacob, E.; Cohen, I.; Shochet, O.; Tenenbaum, A.; Czirók, A.; Vicsek, T. *Phys. Rev. Lett.* **1995**, *75*, 2899-2902.

[4] (a) Pizzarello, S. *Acc. Chem. Res.* **2006**, *39*, 231-237. (b) Cordova, A.; Engqvist, M.; Ibrahem, I.; Casas, J.; Sunden, H. *Chem. Commun.* **2005**, 2047-2049. (c) Bailey, J. *Acta Astronautica* **2000**, *46*, 627-631. (d) Bonner, W.A. *Orig. Life Evol. Biosphere* **1991**, *21*, 59-111. (e) Mason, S.F. *Nature* **1985**, *314*, 400-401.

[5] (a) Lipmann, F.; Hotchkiss, R.D.; Dubois, R.J. *J. Biol. Chem.* **1941**, *141*, 163-169. (b) Gross, E.; Morell, J.L. *J. Am. Chem. Soc.* **1971**, *93*, 4634-4635. (c) Kreil, G. *J. Biol. Chem.* **1994**, *269*, 10967-10970. (d) Heck, S.D.; Siok, C.J.; Krapcho, K.J.; Kelbaugh, P.R.; Thadeio, P.F.; Welch, M.J.; Williams, R.D.; Ganong, A.H.; Kelly, M.E.; Lanzetti, A.J. *Science* **1994**, *266*, 1065-1068.

[6] Triggle, D.J. *Drug Discovery Today* **1997**, *2*, 138-147.

[7] Eichelbaum, M.; Gross, A.S. *Adv. Drug. Res.* **1996**, *28*, 1-64.

[8] (a) Shallenberger, R.S. *Pure Appl. Chem.* **1997**, *69*, 659-666. (b) van der Heijden, A. *Pure & Appl. Chem.* **1997**, *69*, 667-674.

[9] Fabro, S.; Smith,R.L.; Williams, R.T. *Nature* **1967**, *215*, 296-297.

[10] Reist, M.; Carrupt, P.A.; Francotte, E.; Testa, B. *Chem. Res. Toxicol.* **1998**, *11*, 1521-1528.

[11] FDA's Policy Statement for the Development of New Stereoisomeric Drugs (Stereoisomeric Drug Policy) *Fed. Regist.* **1992**, 57 FR22249.

[12] Hargittai, M. *Struct. Chem.* **2006**, *17*, 455-457.

[13] Lee, T.; Yang, C. *Phys. Rev.* **1956**, *104*, 254-258.

[14] (a) Wu, C.S; Ambler, E.; Hayward, R.W.; Hoppes, D.D.; Hudson, R.P. *Phys. Rev.* **1957**, *105*, 1413-1415. (b) Garwin, R.L.; Lederman, L.; Weinrich, M. *Phys. Rev.* **1957**, *105*, 1415-1417. (c) Friedman, J.I.; Telegdi, V.L. *Phys. Rev.* **1957**, *105*, 1681-1682.

[15] Christenson, J.H.; Cronin, J.W.; Fitch, V.L.; Turlay, R. *Phys. Rev. Lett.* **1964**, *13*, 138-140.

[16] Quack, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4618-4630.

[17] Noorduin, W.L.; Izumi,T.; Millemaggi, A.; Leeman, M.; Meekes, H.; Van Enckevort, W.J.P.; Kellogg, R.M.; Kaptein, B.; Vlieg, E.; Blackmond, D.G. *J. Am. Chem. Soc.* **2008**, *130*, 1158-1159. (b) Viedma, C. *Phys. Rev. Lett.* **2005**, *94*, 065504.

[18] (a) Zhang, Y.; Wu, D.-R.; Wang-Iverson, D.B.; Tymiak, A.A. *Drug Discovery Today* **2005**, *10*, 571-577. (b) Maier, N.M.; Franco, P.; Lindner, W. *J. Chromatogr. A* **2001**, *906*, 3-33. (c) Tesarova, E.; Armstrong, D. W. In *Advanced Chromatographic and Elektromigration Methods in Biosciences*; *Journal of chromatography library* - volume 60; Deyl, Z.; Muksik, I.; Tagliaro, F.; Tesarova, E. Eds.; Elsevier, **1998**, pp 197-256.

[19] (a) Pais, L.S.; Rodrigues, A.E. *J. Chromatogr. A* **2003**, *1006*, 33-44. (b) Toumi, A.; Engell, S.; Ludemann-Hombourger, O.; Nicoud, R.M.; Bailly, M. *J. Chromatogr. A* **2003**, *1006*, 15-31.

[20] Perrson, B.A.; Larsson, A.L.E.; Le Ray, M. ; Bäckvall, J.E. *J. Am. Chem. Soc.* **1999**, *121*, 1645-1650.

[21] (a) Joo, H.; Lin, Z.; Arnold, F.H. *Nature* **1999**, *399*, 670-673. (b) Arnold, F.H. *Chem. Eng. Sci.* **1996**, *51*, 5091-5102. (c) Arnold, F.H. *Acc. Chem. Res.* **1998**, *31*, 125-131. (d) Alexeeva, M.; Carr, R.; Turner, N.J. *Org. Biomol. Chem.* **2003**, *1*, 4133-4137. (e) Schoemaker, H.E.; Mink, D.; Wubbolts, M.G. *Science* **2003**, *299*, 1694-1697.

[22] (a) Klibanov, A.M. *Nature* **2001**, *409*, 241-246. (b) Klibanov, A.M. *Trends Biotechnol.* **1997**, *15*, 97-101. (c) Klibanov, A.M. *Nature* **1995**, *374*, 596.

[23] Blaser, H.U.; Spindler, F.; Studer, M. *Appl. Catal., A* **2001**, *221*, 119-143.

[24] Taylor, M.S.; Jacobsen, E.N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5368-5373.

[25] Wyatt, P.; Warren, S. In *Organic Synthesis: Strategy and Control*; Wiley VCH Verlag, Weinheim, **2007.**

[26] Klunder, J.M.; Ko, S.Y.; Sharpless, K.B. *J. Org. Chem.* **1986**, *51*, 3710-3712.

[27] Berkessel, A.; Gröger, H. In *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis.* Wiley VCH Verlag, Weinheim, **2008**.

[28] Movassaghi, M.; Jacobsen, E.N. *Science* **2002**, *298*, 1904-1905.

[29] List, B.; Yang, J.W. *Science* **2006**, *313*, 1584-1586.

[30] (a) List, B. *Tetrahedron* **2002**, *58*, 5573-5590. (b) List, B.; Lerner, R.A.; Barbas III, C.F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

[31] Kagan, H.B. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol.1, pp 9-32.

[32] Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356-5362.

[33] Ohkuma, T.; Kitamura, M.; Noyori, R. In *New Frontiers In Asymmetric Catalysis*; Mikami, K.; Lautens, M. Eds.; Wiley-VCH, **2007**; pp 1-32.

[34] Natta, G. *Makromol. Chem.* **1961**, *43*, 68-75.

[35] Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *7*, 5239-5244.

[36] Osborn, J.A.; Jardine, F.S.; Young, J.F.; Wilkinson, G. *J. Chem. Soc.* **1966**, 1711-1732.

[37] Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942.

[38] Knowles, W.S.; Sabacky, M.J. *Chem. Commun*. **1968**, 1445-1446.

[39] (a) Dang, T.P.; Kagan, H.B. *J. Chem. Soc. D*. **1971**, 481. (b) Kagan, H.B.; Dang, T.P. *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.

[40] Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D.; Weinkauff, D.J. *J. Am. Chem. Soc.* **1975**, *97*, 2567-2568.

[41] Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

[42] Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934.

[43] Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345-350.

[44] Ohta, T.; Takaya, H.; Kitamura, M.; Nagai,K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174-3176.

[45] Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970.

[46] Zhang, W.; Loebach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.

[47] Burk, M.J.; Feaster, J.E.; Harlow, R.L. *Organometallics* **1990**, *9*, 2653-2655.

[48] (a) Rasappan, R.; Laventine, D.; Reiser, O. *Coord. Chem. Rev.* **2008**, *252*, 702-714. (b) Desimoni, G.; Faita, G.; Jørgensen, K.A. *Chem. Rev.* **2006**, *106*, 3561-3651. (c) Gómez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **2008**, *193-195*, 769-835. (d) Ghosh, A.K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45.

[49] Trost, B.M.; Sadahakar, A. *J. Am. Chem. Soc.* **1987**, *109*, 3792-3794.

[50] (a) Knowles, W.S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998-2007. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022. (c) Sharpless, K.B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024-2032.

[51] Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3-16.

[52] Hawkins, J.M.; Watson, T.J..N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3224-3228.

[53] Yoon, T.P.; Jacobsen, E.N. *Science* **2003**, *299*, 1691-1693.

[54] *Chemfiles* **2006**, *6*, 8, 1-15.

[55] Burk, M.J. *Acc. Chem. Res.* **2000**, *33*, 363-372.

[56] (a) Kolb, H.C.; Van Nieuwenzhe, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-2547. (b) Bolm, C.; Jacobsen, E.N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**; pp 399-428.

[57] Negishi, E.-I. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**; pp 165-190.

[58] Seebach, D.; Beck, A.K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138.

[59] Van den Berg, M.; Haak, R.M.; Minnaard, A.J.; de Vries, A.H.M.; de Vries, J.G.; Feringa, B.L. *Adv. Synth. Catal.* **2002**, *344*, 1003-1007.

[60] Desimoni, G.; Faita, G.; Jørgensen, K.A. *Chem. Rev.* **2006**, *106*, 3561-3651.

[61] Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131-147.

[62] Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062-4066.

[63] Handy, S.T. *Curr. Org. Chem.* **2000**, *4*, 363-395.

[64] Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581-1590.

[65] Pfaltz, A.; Drury III, W.J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5723-5726.

[66] Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169-178.

[67] Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336-345.

[68] The turnover number (TON) is the number of moles of substrate that a mole of catalyst can convert before becoming deactivated. An ideal catalyst has an infinite TON because it is never consumed. In reality, this is never the case.

[69] The turnover frequency (TOF) is the number of moles of substrate that is converted by a mole of catalyst per unit time.

[70] Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788-824.

[71] (a) Agranat, I.; Caner, H.; Caldwell, J. *Nat. Rev. Drug Discov.* **2002**, *1*, 753-768. (b) Agranat, I.; Caner, H. *Drug Discovery Today* **1999**, *4*, 313-321. (c) Rouhi, A.M. *C&EN* **2003**, *81*, 56-61. (d) Somogyi, A.; Bochner, F.; Foster, D. *Australian Prescriber* **2004**, *27*, 47-49.

[72] Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discovery Today* **2004**, *9*, 105-110.

[73] (a) Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 17-31. (b) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol.1, pp 1427-1438.

[74] Federsel, H.-J. *Nat. Rev. Drug Discov.* **2005**, *4*, 685-697.

[75] Blaser, H.-U. *Chem. Commun.* **2003**, 293-296.

[76] Harrington, P.J.; Lodewijk, E. *Org. Process. Res. Dev.* **1997**, *1*, 72-76.

2

AIMS AND OUTLINE OF THIS THESIS

Since its first appearance, more than 40 years ago, the field of asymmetric catalysis has known a tremendous evolution. A wide variety of chiral catalysts for a huge number of enantioselective reactions has been developed. This gives the impression that for almost every reaction an enantioselective catalytic variant is available. However, the number of truly useful enantioselective catalysts is still limited. Many of the existing methods still need to be improved and the search for new and better ligands is still ongoing.

The key to efficient asymmetric catalysis is the combination of a metal with a suitable chiral organic ligand. An ideal ligand is easily accessible and has a modular structure that allows rapid diversification. Current approaches in finding new catalysts are still rather empirical in which chance, intuition and a systematic screening play an important role. A purely rational approach is hampered by the lack of mechanistic understanding and the complexity of most catalytic processes.

The development of novel ligand classes can result in the discovery of new reactivities and, as a consequence, give access to new enantiomerically enriched molecules and new enantioselective catalytic processes. Therefore, it remains important to continue the search for new and improved ligands.

In this work, two main ligand classes have been studied: chiral diene ligands and chiral imidate ligands. Both have in common that their use was, until recently, precluded from asymmetric catalysis due to their presumed instability. The use of chiral dienes was neglected because of their easy dissociation from the metal. However, dienes with the proper geometry can form very stable complexes. In contrast, the use of imidates was delayed by their assumed intrinsic instability. Imidates are mostly used as synthetic building blocks and sometimes as pharmacophoric groups.

In chapter 3, we discuss the synthesis of chiral bicyclo[2.2.1]heptadiene ligands **2.2** via a novel route starting from an enantiomerically pure vinylic bistriflate **2.1** (Figure 2.1). This work was stimulated by the synthesis of DIPHONANE in our laboratory

where the same bistriflate **2.1** was used as a key intermediate.[1] Use of this bistriflate **2.1** resulted into a more versatile route towards these chiral norbornadiene ligands[2] **2.2** as compared to the original route described by Hayashi *et al.*[3] These ligands were tested in several rhodium-catalyzed reactions.

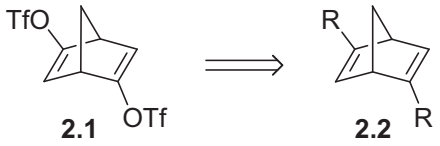


Figure 2.1. *Synthesis of chiral diene ligands via a vinylic bistriflate.*

In chapter 4, we report on the synthesis and application of imidates as a new nitrogen-based ligand class. This type of ligands has not yet been described in literature and is therefore extremely interesting. Starting from a central building block **2.3**, a small ligand library could be synthesized. We synthesized C_1 and C_2 – symmetrical imidate ligands (**2.4** and **2.5**), as well as hybrid imidate, phosphane ligands **2.6** (Figure 2.2).[4,5] These ligands were evaluated in several asymmetric metal-catalyzed reactions.

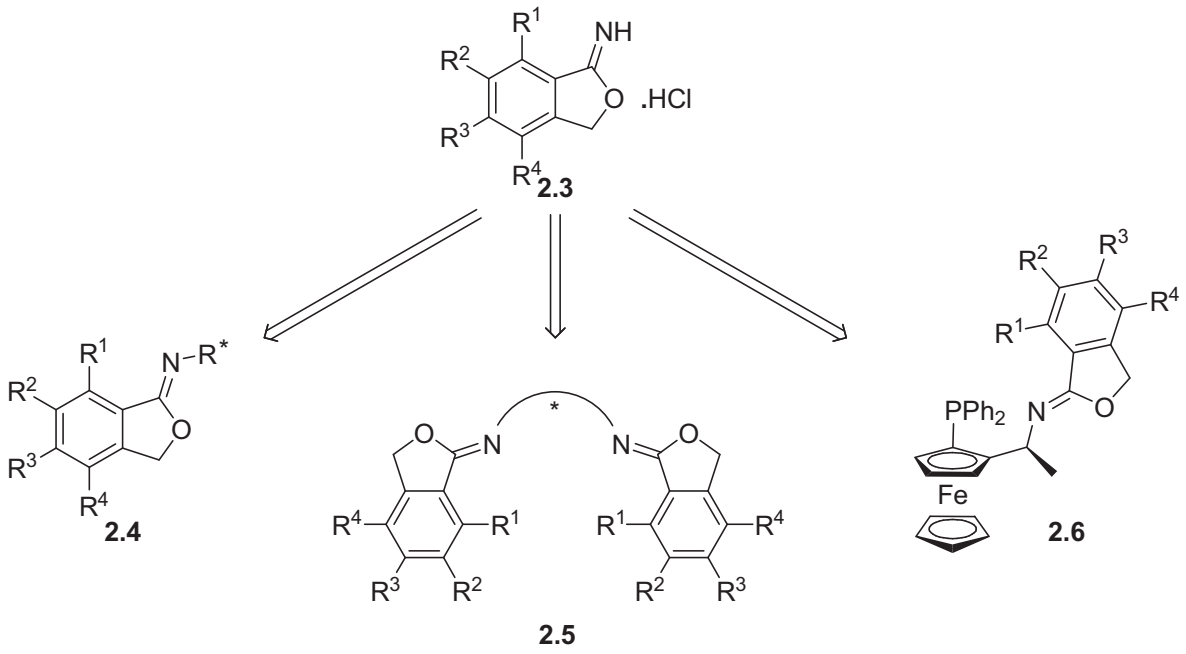


Figure 2.2. *Synthesis of an imidate ligand family: C_1-symmetrical (**2.4**), C_2-symmetrical (**2.5**) and hybrid imidate,phosphane ligands (**2.6**).*

The imidate ligand precursor **2.3** is also an interesting synthetic building block for other N-based ligands. This compound was used in the synthesis of chiral oxazoline-alcohol ligands **2.7**[6] and chiral imidazolidines **2.8** (Figure 2.3).

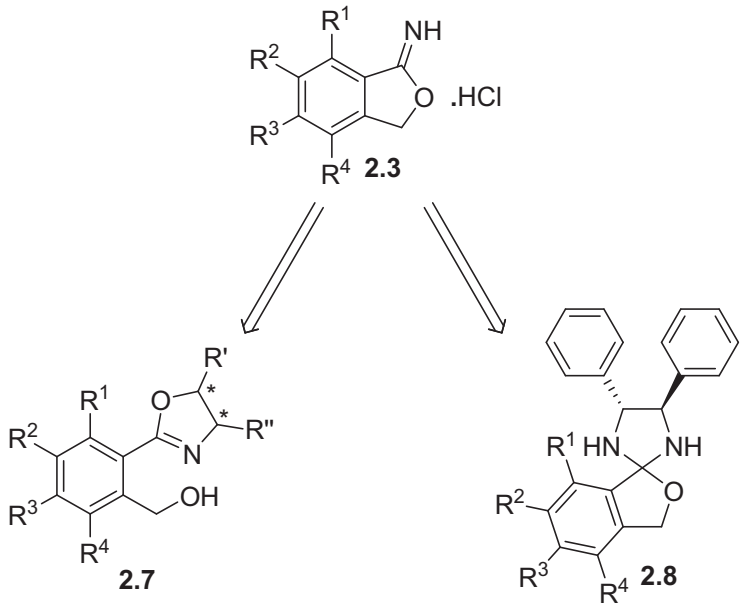


Figure 2.3. *Synthesis of chiral oxazoline-alcohol ligands (**2.7**) and chiral imidazolidines (**2.8**).*

REFERENCES

[1] Vandyck, K.; Matthys, B.; Willen, M.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Org. Lett.* **2006**, *8*, 363-366.

[2] Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967.

[3] Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.

[4] Noël, T.; Vandyck, K.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Tetrahedron* **2009**, *65*, 8879-8884.

[5] Noël, T.; Bert, K.; Van der Eycken, E.; Van der Eycken, J. **2009** (submitted for publication).

[6] Noël, T.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.; Van der Eycken, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1962-1968.

3

CHIRAL DIENE LIGANDS

3.1 INTRODUCTION

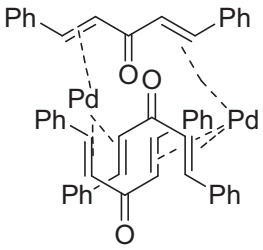
In 1827, Zeise synthesized one of the first organometallic compounds: the platinum complex **3.1**, containing an ethylene molecule (Figure 3.1).[1]

3.1

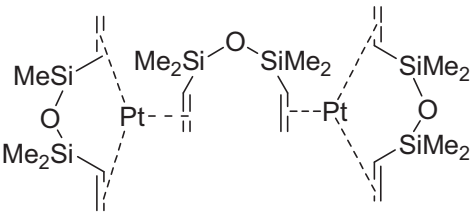
Figure 3.1. *Zeise's salt.*

Ever since, the use of olefin ligands in transition metal chemistry has become very important. Olefin ligands are known as labile ligands. Most of the time, they serve as "placeholders" for vacant coordination sites for ligand exchange reactions with stronger binding ligands, such as phosphanes and nitrogen ligands. Sometimes, olefin ligands also fulfil more complex functions in transition metal catalysis.[2] Olefin ligands facilitate reductive elimination over β-hydride elimination. The coordination of olefins to the metal fills the vacant coordination sites which are necessary for the β-hydride elimination. Since olefin ligands are labile ligands, they easily dissociate from the metal and hence promote oxidative addition. Olefins can also influence the product selectivity.

Noteworthy are $Pd_2(dba)_3$ (**3.2**) and $Pt_2(dvds)_3$ (**3.3**). The first catalyst is a well-known precursor for cross-coupling reactions.[3] The latter is also known as Karstedt's catalyst and is used in hydrosilylation reactions (Figure 3.2).[4]



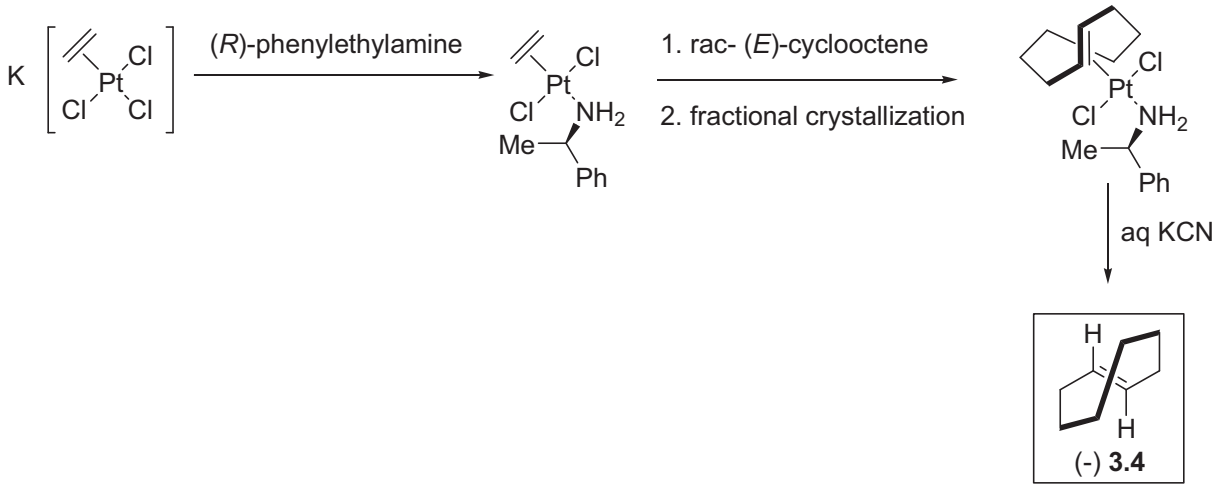
$Pd_2(dba)_3$
3.2



$Pt_2(dvds)_3$
Karstedt catalyst
3.3

Figure 3.2. *Olefin-containing transition-metal complexes: $Pd_2(dba)_3$ and Karstedt's catalyst.*

The first chiral olefin was synthesized by Cope *et al*.[5] (*E*)-cyclooctene (**3.4**) shows planar chirality and was obtained in an enantiomerically pure form via a fractional crystallization of diastereomeric Pt complexes (Scheme 3.1).



Scheme 3.1. *Synthesis of chiral (E)-cyclooctene.*

3.2 THE METAL-OLEFIN BONDING[6,7]

The chemical bonding between an olefin and a transition metal is usually described via the Dewar-Chatt-Duncanson model (Figure 3.3).[8] According to this model, a σ-bond is formed between the π_{2p} orbital of the olefin and an empty d orbital of the metal. The π electrons of the olefin are donated to the metal (L→M donation, d). This is accompanied by back donation of electrons from a filled d orbital of the metal to the empty π_{2p}^* orbital of the alkene (M→L back-donation, b). On binding, the C=C bond of the olefin lengthens. This is mainly caused by the back-donation (b) and results in a rehybridization of the coordinated olefin carbons from sp^2 to sp^3. This explains why strained alkenes bind very strongly to metals; as in these cases rehybridization leads to a relief of strain.

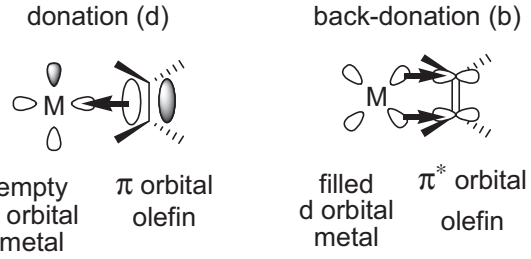
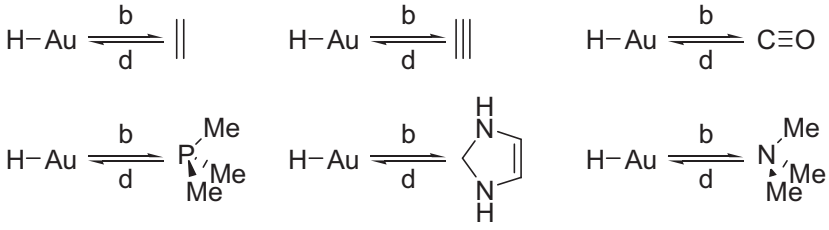


Figure 3.3. *Dewar-Chatt-Duncanson Model*

Frenking *et al.* developed a partitioning scheme for analyzing the donor-acceptor interactions in a complex, called charged decomposition analysis (CDA).[9] The CDA can be used as a quantitative expression of the Dewar-Chatt-Duncanson model. It calculates the relative amount of electron donation (d) and back-donation (b) in transition metal complexes for different ligands and metals. The orbital contributions to the charge distribution are divided in 4 parts:

1) mixing the occupied orbitals of the ligand and the unoccupied MO's of the metal fragment (L→M donation, d);
2) mixing the unoccupied orbitals of the ligand and the occupied MO's of the metal fragment (M→L back-donation, b);
3) mixing the occupied orbitals of the ligand and the occupied MO's of the metal fragment (L↔M repulsive polarization, r);
4) mixing the unoccupied orbitals of the ligand and the unoccupied MO's of the metal fragment (residual term Δ). The residual term Δ should be ~0 for true donor-acceptor complexes. Thus the residual term Δ serves as a control term.

In table 3.1 CDA results are given for some HAu-L complexes. Some interesting conclusions can be drawn. The data show that olefins are quite good donors comparable to *N*-heterocyclic carbenes (NHC). Phosphanes are the strongest, while acetylene and amines are weak donors. The acceptor properties of olefins are again comparable with NHCs. Phosphanes are very good acceptors. Amines are the weakest acceptors, as a result the d/b ratio becomes very large.



Ligand (L)	d	b	d/b
C_2H_4	0.36	0.13	2.9
C_2H_2	0.16	0.12	1.3
CO	0.27	0.22	1.2
PMe_3	0.53	0.16	3.3
imidazol-2-ylidene	0.36	0.12	3.0
NMe_3	0.20	0.01	32.7

Table 3.1. *CDA analyses for some HAu-L complexes. All energies are in kcal.mol^{-1}.*

A second important method is the extended transition state (ETS) promoted by Ziegler and Rauk.[10] It is an energy partitioning method which calculates the energies associated with the ligand→metal donation and the metal→ligand back-donation. The bond dissociation energy $-D_e$ between two fragments A and B is partitioned into several contributions. First, $-D_e$ is separated into two major components ΔE_{prep} and ΔE_{int}:

$$-D_e = \Delta E_{prep} + \Delta E_{int} \qquad (1)$$

ΔE_{prep} is the energy needed to promote the fragments A and B from their equilibrium geometry and electronic ground state to the geometry and electronic state in the compound AB. ΔE_{int} is the interaction energy between the two fragments in the molecule. This component can be divided on his part in three more components:

$$\Delta E_{int} = \Delta E_{elstat} + \Delta E_{Pauli} + \Delta E_{orb} \qquad (2)$$

ΔE_{elstat} gives the electrostatic interaction energy between the two fragments. ΔE_{Pauli} is a component giving the repulsive interactions between the fragments due to the fact that two electrons with the same spin cannot occupy the same region in space. ΔE_{orb} is the stabilising orbital interaction term. The ΔE_{elstat} term can be associated with the ionic bonding and ΔE_{orb} with the covalent contributions to the bond.[11] In table 3.2 these energies are shown for the HAu-L complexes.

Ligand (L)	ΔE_{int}	ΔE_{elstat}	ΔE_{Pauli}	ΔE_{orb}
C_2H_4	-27.6	116.5	-90.9	-53.2
C_2H_2	-26.6	118.5	-91.4	-53.8
CO	-34.2	154.2	-120.3	-68.1
PMe_3	-43.8	153.5	-144.3	-53.0
imidazol-2-ylidene	-52.7	174.1	-173.3	-53.5
NMe_3	-29.9	82.5	-81.7	-30.7

Table 3.2. *ETS analyses for some HAu-L complexes. All energies are in kcal.mol^{-1}.*

It is clear that the ΔE_{orb} is similar for all ligands except the CO and amine ligand; this shows that this term should be carefully used in the context of complex stabilities. The repulsive term ΔE_{Pauli} is not counterbalanced with ΔE_{elstat} in the case of olefin, acetylene and CO ligands. In the case of NHC, the attractive term ΔE_{elstat} is almost completely neutralized by the repulsive term ΔE_{Pauli}. This makes that NHCs, together with phosphanes, are the strongest ligands in this series.

Grützmacher *et. al.* investigated the influence of substituents on the donation and back-donation in the bonding of both olefin and phosphine ligands with a platinum metal via CDA and ETS.[12] In table 3.3 the most important data are represented. For the olefin ligands, it is clear that neither the donation (d) nor the back-donation (b) depends largely on the nature of the substituent R. However, when we look at the d/b ratios some trends become clear. The acrylonitrile is the strongest acceptor while the enol is the strongest donor olefin. In phosphanes, again the d/b ratio is high. This means that electron donation makes a significant contribution to the binding. The most important conclusion we can draw from this table, is that variation of the

substituents R has a larger effect in the phosphane complexes. This indicates that the electronic properties of a transition-metal complex may be more easily controlled by changing the substituent of a coordinated phosphane than in an olefin complex.

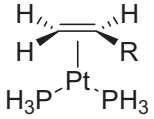
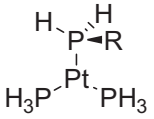
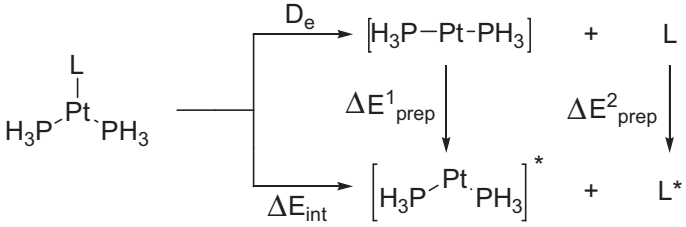
	R	d	b	d/b	Δ	D_e	ΔE_{int}
	H	0.51	0.38	1.33	-0.01	15.4	56.9
	CN	0.47	0.42	1.13	-0.01	17.6	62.8
	F	0.51	0.40	1.27	-0.02	11.9	58.9
	NH2	0.51	0.38	1.35	-0.02	6.6	54.7
	OH	0.50	0.37	1.37	-0.02	9.9	53.9
	H	0.38	0.23	1.67	0.02	9.7	28.3
	CN	0.35	0.29	1.20	0.02	11.4	30.1
	F	0.46	0.34	1.35	-0.04	19.6	44.3
	NH2	0.49	0.27	1.78	0.01	14.2	35.8
	OH	0.47	0.30	1.53	0.00	16.3	38.7

Table 3.3. *CDA and ETS analysis of Pt-olefin and Pt-phosphane complexes. All energies are in kcal.mol^{-1}.*

The dissociation energy D_e is the energy which is required to dissociate the complex $Pt(PH_3)_2L$ into the fragments $Pt(PH_3)_2$ and L. Both fragments should be in their ground state structures, i.e. $Pt(PH_3)_2$ being linear and the ligand L in the uncomplexed structure (scheme 3.2).



Scheme 3.2. *Illustration of the dissociation energy (D_e), the interaction energy (ΔE_{int}) and the preparation energies (ΔE^1_{prep} and ΔE^2_{prep}).*

The dissociation energy D_e is smaller than the interaction energy ΔE_{int} by the sum of the preparation energies ΔE^1_{prep} and ΔE^2_{prep}:

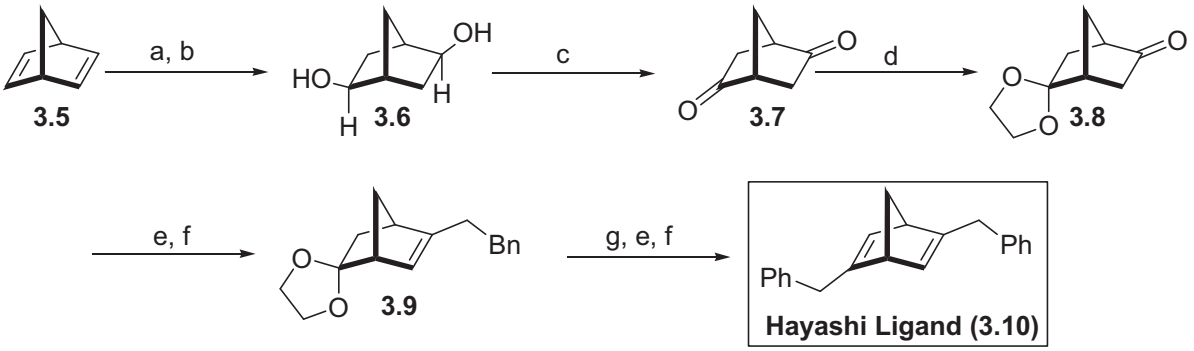
$$D_e = \Delta E_{int} - (\Delta E^1_{prep} + \Delta E^2_{prep}) \qquad (3)$$

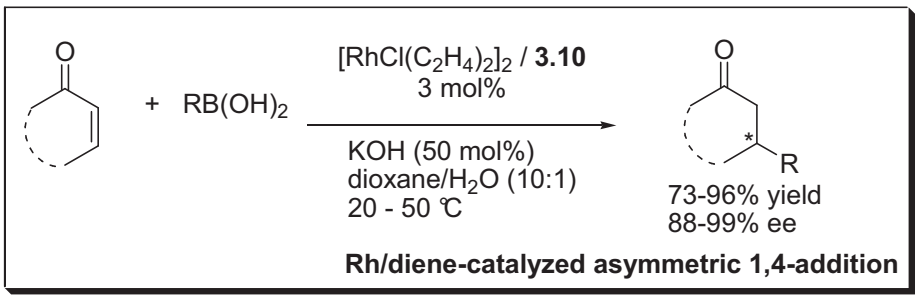
Most of the time, D_e and ΔE_{int} do not differ too much from each other, e.g. when only small deviations are needed to prepare the “ready-to-bind” states MX2* and L*. However, it is clear from table 3.3 that ΔE^2_{prep} are especially large for olefin ligands. This is due to the elongation of the double bond and rehybridization of the carbon atoms from sp^2 to sp^3 upon complexation. This is the reason why olefin ligands are relatively weakly bonded ligands.

3.3 CHIRAL OLEFIN LIGANDS IN ASYMMETRIC TRANSITION-METAL CATALYIS[7,13]

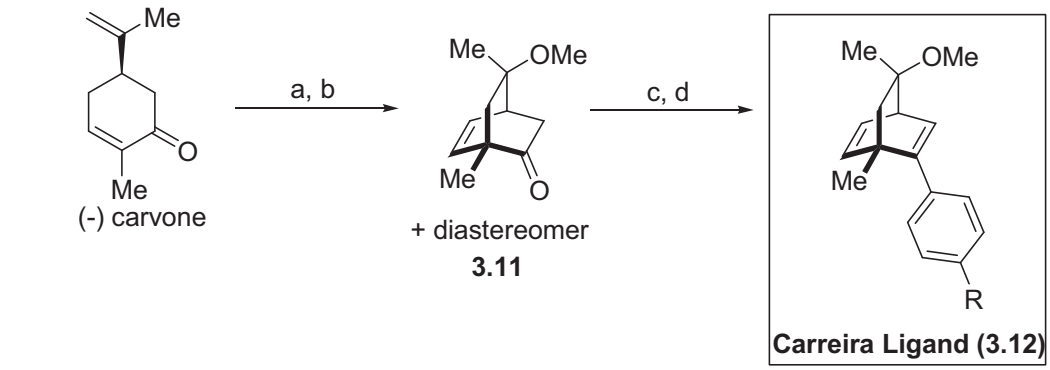
Whereas olefins have been used as ligands since the emergence of Zeise's salt, the use of chiral olefin ligands in asymmetric transition metal catalysis has long been neglected. This was mainly due to the observed lability of olefin ligands. Lemaire observed that the nature of an achiral diene had a great influence on the asymmetric reduction of ketones.[14] He also stated that it is worthwhile to study complexes with a chiral diene. This idea was, however, not immediatly put into practice.

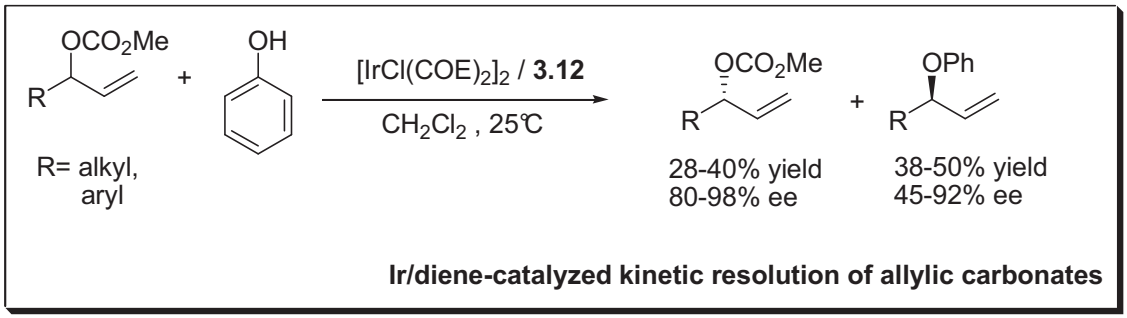
In 2003, the first chiral diene ligand was disclosed by Hayashi *et al*.[15] He synthesized a C_2-symmetrical diene (**3.10**) based on a rigid bicyclo[2.2.1]heptadiene framework. The catalytic activity exerted by the chiral olefin-rhodium complex in asymmetric 1,4-additions was one of the highest observed. In addition, very high selectivities were obtained (up to 97% ee) (Scheme 3.3).
This work was rapidly followed by a publication from Carreira's group.[16] Independent from the work of Hayashi, Carreira *et al.* synthesized a chiral diene based on a bicyclo[2.2.2]octadiene backbone (**3.12**). They evaluated the catalytic properties of this diene in the iridium-catalyzed kinetic resolution of allyl carbonates. Again very high enantioselectivities were obtained (Scheme 3.4).
It is entirely clear that the synthesis of Carreira's ligand has some advantages over Hayashi's synthesis. Firstly, the synthesis is much shorter and starts from cheap carvone. Secondly, introduction of side chains is not straightforward in the case of Hayashi, due to the sequential introduction of the two side chains.





Scheme 3.3. *Synthesis of Hayashi's ligand (**3.10**): a) $HSiCl_3$, $[PdCl(\pi\text{-allyl})]_2$/ (R)-MeO-MOP (0.1 mol% Pd), 0℃. b) i)MeOH, Et_3N; ii) H_2O_2, KHF_2, THF/MeOH. c) Swern conditions. d) $HOCH_2CH_2OH$, TsOH. e) i) LDA, THF; ii) Tf_2Npy-2. f) $BnMgBr/Et_2O$, $PdCl_2(dppf)$ (1 mol%). g) dil HCl/THF.*

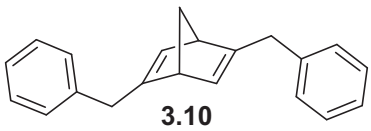




Scheme 3.4. *Synthesis of Carreira's ligand (**3.12**): a) NBS, MeOH. b) t-BuOK, t-BuOH. c) LDA, $PhNTf_2$. d) ArZnCl, cat Pd.*

The pioneering work of Hayashi and Carreira demonstrates that dienes with the proper geometry can be used as stable ligands for asymmetric transition metal catalysis. Since then a large number of chiral olefin ligands has been synthesized by various groups (Figure 3.4). The most intriguing examples will be discussed in more detail.

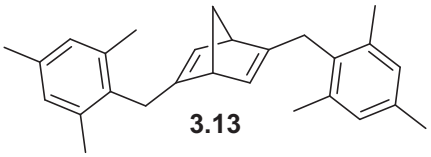
2003



3.10

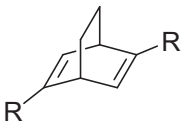
Hayashi[15]

2004



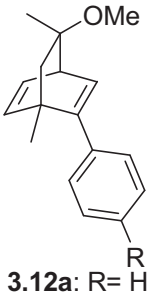
3.13

Hayashi[17]



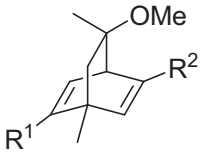
3.14a: R= Ph
3.14b: R= Bn

Hayashi[18]



3.12a: R= H
3.12b: R= Ph
3.12c: R= OPh
3.12d: R= *t*-Bu

Carreira[16]



3.15a: R^1= *i*-Bu and R^2= allyl
3.15b: R^1= Ph and R^2= Bn
3.15c: R^1= Ph and R^2= allyl
3.15d: R^1= Ph and R^2= n-Prl
3.15e: R^1= Ph and R^2= 3-butenyl

Carreira[19]

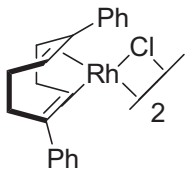
2005

3.16

Hayashi[20]

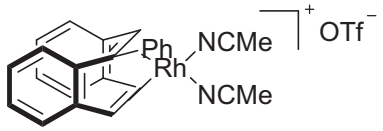
3.17

Hayashi[21, 22]



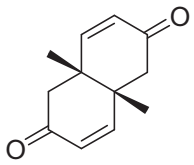
3.18

Hayashi[23]



3.19

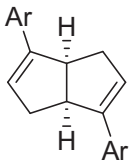
Grützmacher[24]



3.20

Trauner[25]

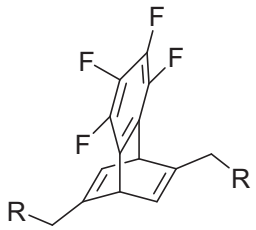
2007



3.21a: Ar= Ph
3.21b: Ar= Bn
3.21c: Ar= *p*-Me-O-Ph
3.21d: Ar= 1-naphthyl

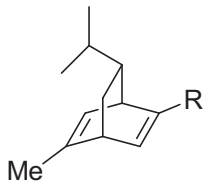
Xu & Lin[26]
Laschat[27]

2008



3.22a: R= OCH_2OCH_3
3.22b: R= OH
3.22c: R= Ph
3.22d: R= $OSiPh_3$
3.22e: R= (-)-menthoxy

Hayashi[28, 29]

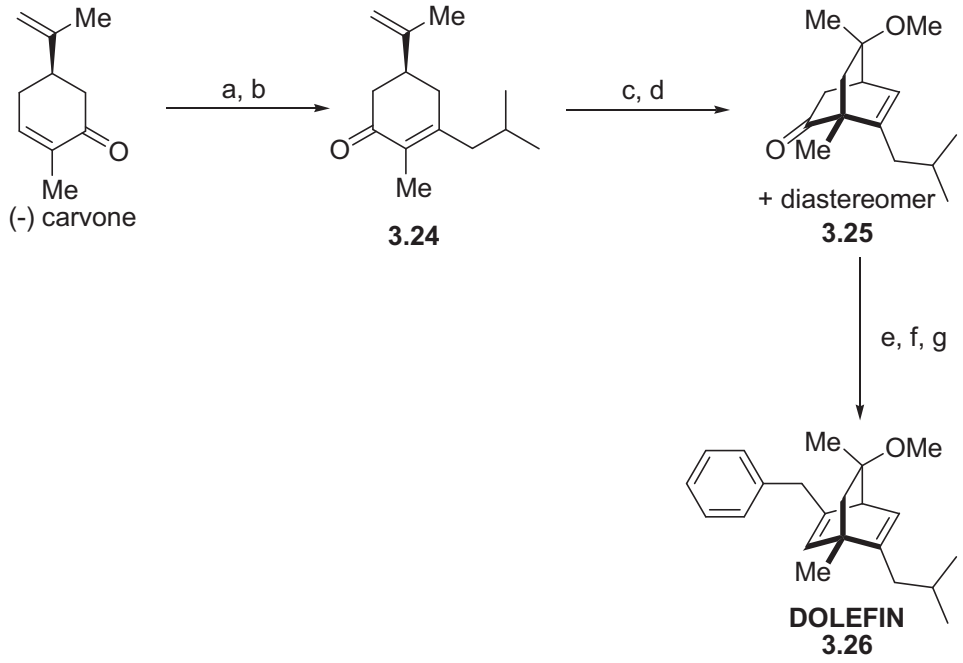


3.23a: R= CO_2Me
3.23b: R= CH_2OH
3.23c: R= CH_2OMe
3.23d: R= CMe_2OH
3.23e: R= CMe_2OMe

Hayashi[30]

Figure 3.4. *Overview of the chiral dienes synthesized by various groups.*

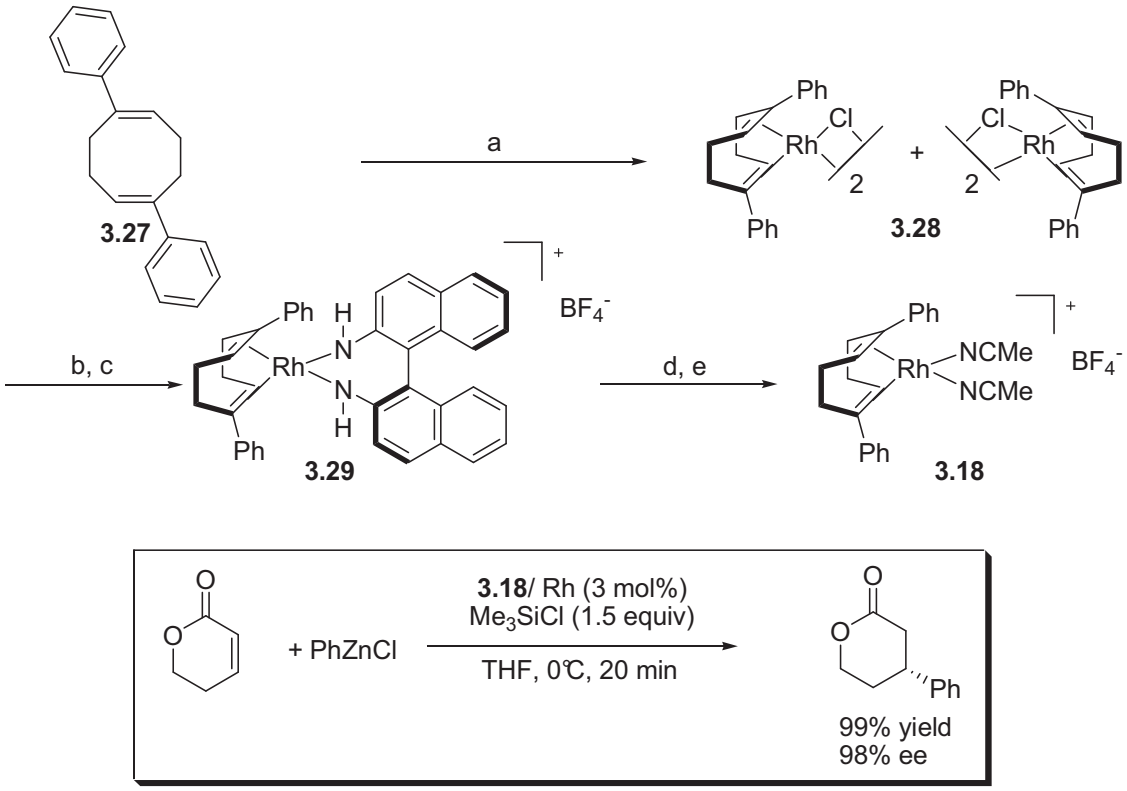
Shortly after their first paper, Carreira *et al.* synthesized a novel diene ligand (**3.15a-e**).[19] Via a slight modification of the original synthetic route, two substituents could be introduced (Scheme 3.5). The most successful member of this ligand class is commercially available in both enantiomeric forms from Sigma-Aldrich under the name DOLEFIN (**3.26**). These ligands were used for asymmetric 1,4-addition to α, β-unsaturated carbonyl compounds and to α, β-unsaturated aldehydes.



Scheme 3.5. *Synthesis of Carreira's disubstituted DOLEFIN (**3.26**): a) i-BuMgBr, Et_2O. b) PCC, CH_2Cl_2. c) NBS, CH_2Cl_2, MeOH. d) t-BuOK, THF. e) i) LDA, THF; ii) BnBr. f) $LiNEt_2$, $PhNTf_2$, THF. g) $Pd(OAc)_2$, Ph_3P, HCO_2H, DMF.*

Hayashi *et al.* synthesized a whole range of bicyclic dienes. The bicyclo[2.2.2]octadiene ligand (**3.14a-b**) was resolved through a fractional crystallization of a hydrazone in very low yield which is a major drawback of this ligand family.[18] The bicyclo[3.3.1]nonadiene (**3.16**) and bicyclo[3.3.2]decadiene (**3.17**) ligands were resolved via preparative HPLC on a chiral stationary phase.[22] The low yield for the recrystallization and the use of preparative HPLC techniques for the separation of ligands can seriously hamper their use in both university and industry.

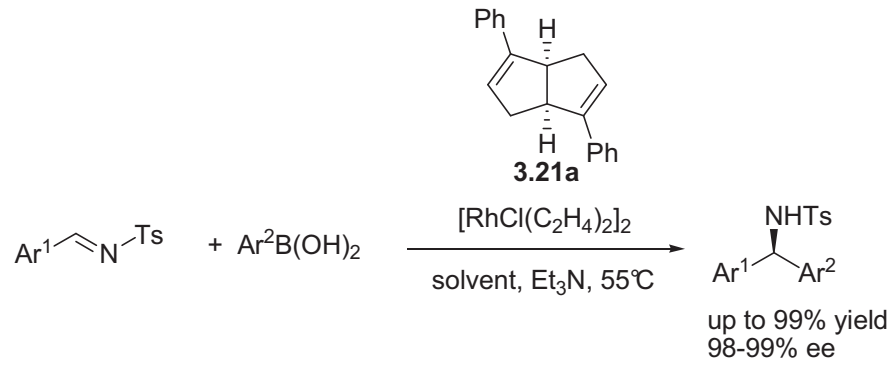
A very elegant method for the separation of chiral ligands was demonstrated by Grützmacher *et al*.[24] and later by Hayashi *et al* (Scheme 3.6).[23] The chirality of the prochiral diene (**3.27**) is generated and fixed on coordination to the metal (**3.28**). Ligand substitution with (*R*)-1,1'-binaphthyl-2,2'-diamine formed a mixture of diastereomeric complexes (**3.28**). Fractional crystallization yielded selectively one of the diastereomeric isomers (**3.29**). Removal of the chiral diamine with HCl in acetonitrile followed by abstraction of the chloride with $AgBF_4$ afforded the enantiomerically pure complex (**3.18**). This complex **3.18** was used in the rhodium-catalyzed asymmetric 1,4-addition. It appeared that the enantioselectivity was lower when higher conversions were obtained. This was due to the racemization of the catalyst under the reaction conditions. They realized that if one could find conditions making the addition step faster than the catalyst racemization, higher selectivities could be obtained. By using phenylzinc chloride in the presence of chlorotrimethylsilane - which is a very fast reaction[31] - high enantioselectivities were obtained.



Scheme 3.6. *Resolution of a substituted cyclooctadiene (**3.27**) by complexation with a chiral diamine: a) $[RhCl(C_2H_4)_2]_2$, benzene . b) i) (R)-1,1'-binaphthyl-2,2'-diamine; ii) $AgBF_4$, CH_2Cl_2. c) recrystallization in THF/benzene. d) conc HCl, MeCN. e) $AgBF_4$, MeCN.*

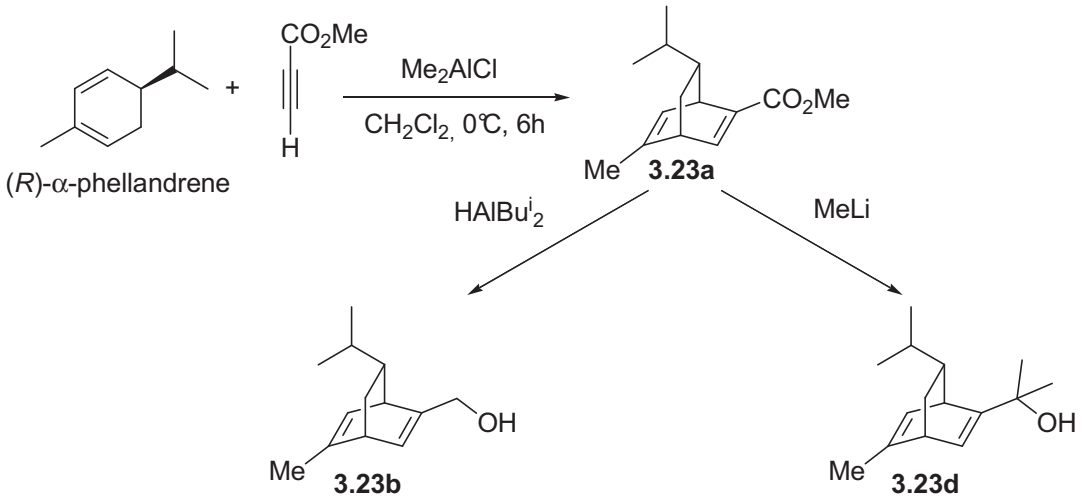
Trauner *et al.* synthesized a bisenone (**3.20**) that formed an air- and moisture-insensitive, stable Pd(0)-complex.[25] Unfortunately, the complex did not show any asymmetric induction.

Xu and Lin developed a new chiral diene ligand class based on a bicyclo[3.3.0]-2,6-octadiene framework (**3.21a-d**).[26] This C_2-symmetrical tetrahydropentalene-rhodium catalytic system showed remarkable yields and enantioselectivities (98-99% ee) in the addition of a wide range of arylboronic acids to imines (Scheme 3.7). This ligand is now commercially available from Sigma-Aldrich.



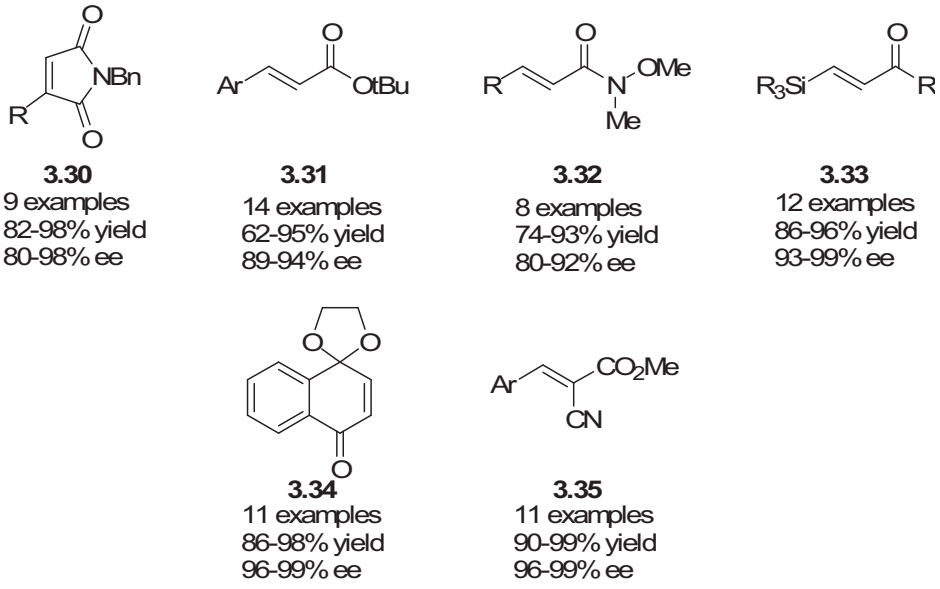
Scheme 3.7. *Catalytic asymmetric 1,2-addition of arylboronic acids to N-tosylarylimines.*

In an efficient way, Hayashi *et al.* developed a new diene ligand (**3.23a**) in one step via a [4+2] cycloaddition of (*R*)-α-phellandrene with methyl propiolate in 73% yield.[30] Several analogues (**3.23b-e**) could be synthesized from this diene (Scheme 3.8). High selectivities were obtained with this ligand in rhodium-catalyzed asymmetric conjugate addition reactions.



Scheme 3.8. *Easy one-step synthesis of chiral dienes.*

As already mentioned, asymmetric conjugate additions are very suitable reactions for diene catalyst systems. Several substrates have been addressed by various groups, e.g. substituted maleimides[32] (**3.30**), α,β-unsaturated esters[33] (**3.31**), α,β-unsaturated Weinreb amides[34] (**3.32**), β-silyl-substituted- α,β-unsaturated carbonyl compounds[35] (**3.33**), quinone monoketals[36] (**3.34**) and arylmethylene cyanoacetates[37] (**3.35**) (Figure 3.5).



3.30
9 examples
82-98% yield
80-98% ee

3.31
14 examples
62-95% yield
89-94% ee

3.32
8 examples
74-93% yield
80-92% ee

3.33
12 examples
86-96% yield
93-99% ee

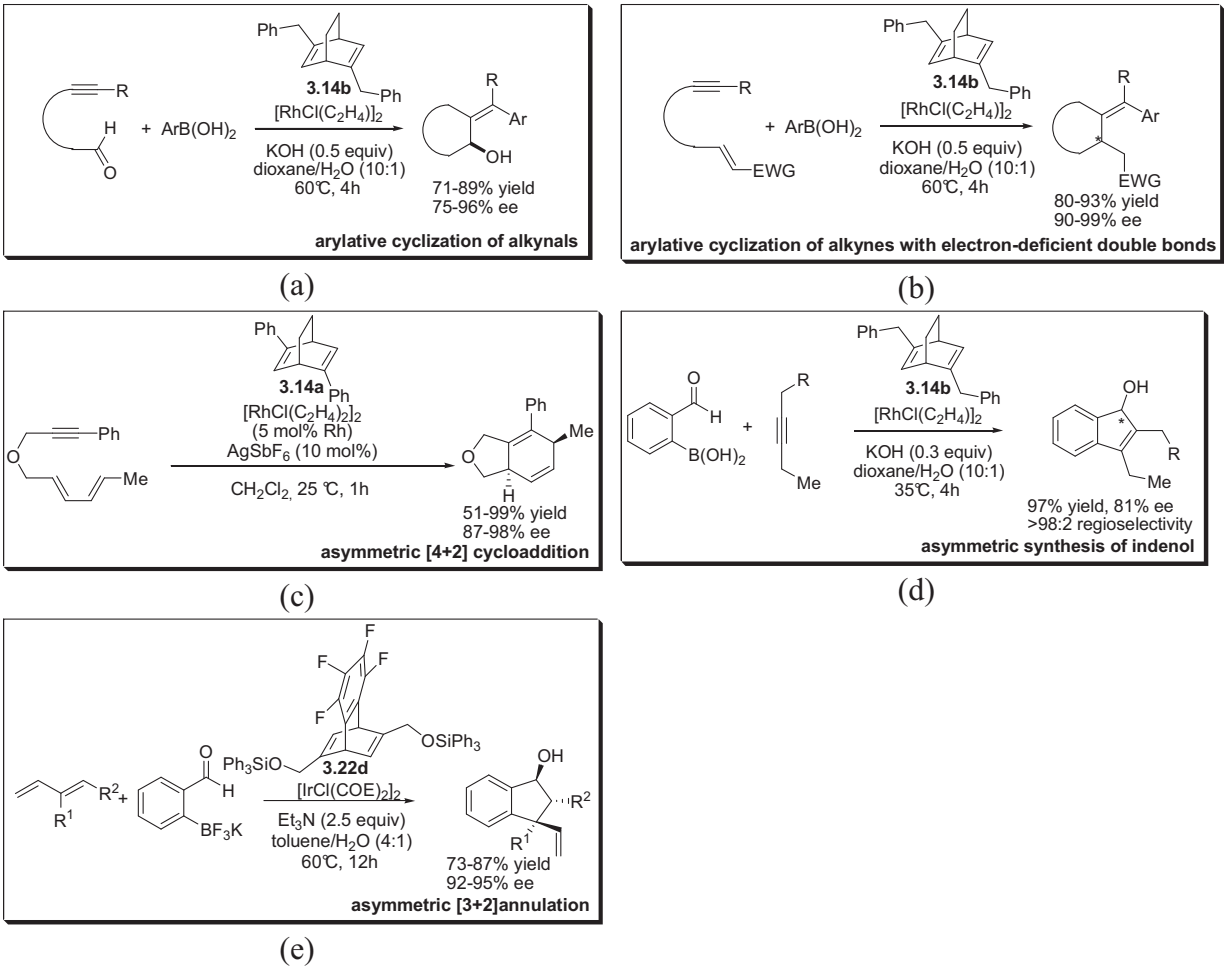
3.34
11 examples
86-98% yield
96-99% ee

3.35
11 examples
90-99% yield
96-99% ee

Figure 3.5. *Different acceptors in Rh/diene-catalyzed 1,4-additions.*

Chiral diene-metal complexes can even catalyze efficiently domino reactions. Domino reactions, or cascade reactions, are processes involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.[38,39] These domino reactions are very powerful methods for the preparation of structurally complex molecules in a convergent manner from relatively simple precursors. Hayashi *et al.* evaluated the effectiveness of chiral diene ligands in several cascade reactions (Scheme 3.9).
For example, the organorhodium species can undergo a *syn* addition across the triple bond of alkynals.[40] The formed intermediate readily cyclizes by an intramolecular attack on the aldehyde. The resulting cyclic allylic alcohols were obtained in high yield and selectivity (Scheme 3.9a). In the presence of (*S*)-BINAP, low yields are obtained and only moderate selectivities (24% yield, 76% ee).
Remarkable chemoselectivity was observed when alkyne-tethered electron-deficient olefins were used as substrates.[41] Using bisphosphanes, such as (*S*)-BINAP and dppf, the 1,4 addition was more effectively catalyzed than the arylation of alkynes. A low chemoselectivity was observed with (*S*)-BINAP resulting in various products. In contrast, Rh/diene (**3.14b**) catalysts favor effectively the arylation of alkynes and high selectivities were obtained (Scheme 3.9b).
A rhodium-chiral diene complex (**3.14a**) served as a high-performance catalyst for the intramolecular asymmetric [4+2] cycloaddition of alkyne-1,3-dienes.[42] A rhodium-COD complex was 20 times more active than a rhodium-bisphosphane complex: (*R*, *R*)-Me-DUPHOS gave only 9% yield and 44% ee (Scheme 3.9c).

Also indenols could be synthesized in high yield and good selectivity.[43] The same reaction with phosphane ligands failed to produce the desired product (Scheme 3.9d).
Attempts to synthesize indanols with diene ligand (**3.14b**) all failed. In contrast, higher activities of the rhodium-complex were obtained with the tetrafluorobenzobarrelene (tfb) ligands (Scheme 3.9e).[44] In equilibrium experiments between both diene ligands and their iridium complexes, a higher coordination ability was observed for the tfb ligand.



Scheme 3.9. *Overview of diene/metal-catalyzed cascade reactions.*

Recently, several groups designed phosphane-olefin hybrid ligands (Figure 3.7). These ligands combine the high coordination ability of phosphane ligands and the good chiral environment created around the metal by olefin ligands (Figure 3.6). The two groups on phosphorus shield both the top-left and bottom-left sections of the space around the metal, while the group on the olefin blocks only the top-right section.

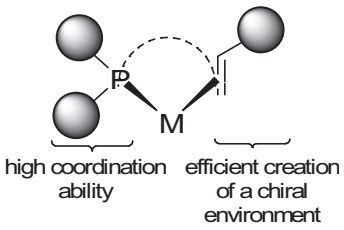
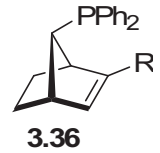
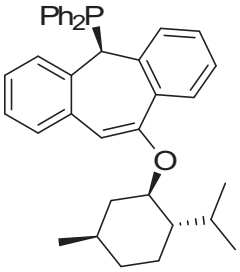


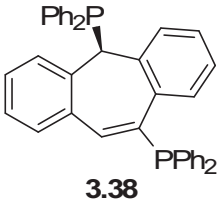
Figure 3.6. *Design of chiral phosphane-olefin ligands.*



3.36

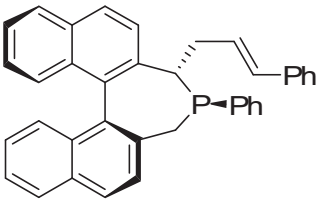


3.37



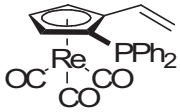
3.38

Hayashi[45]



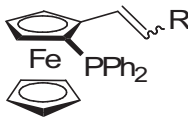
3.39

Widhalm[48]



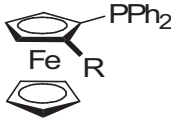
3.42

Grützmacher[46]



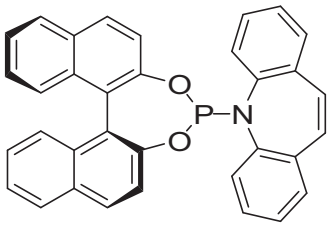
3.40a-c
R= H, Me, Ph

Stepnicka[49]



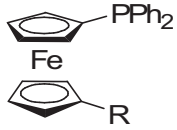
3.43a-b

Grützmacher[47]



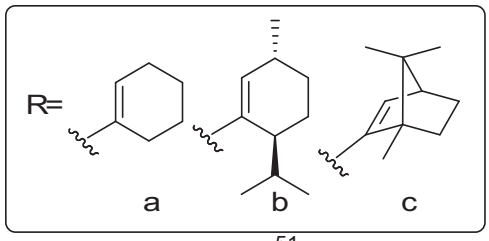
3.41

Carreira[50]



3.44b-c

Bolm[51]



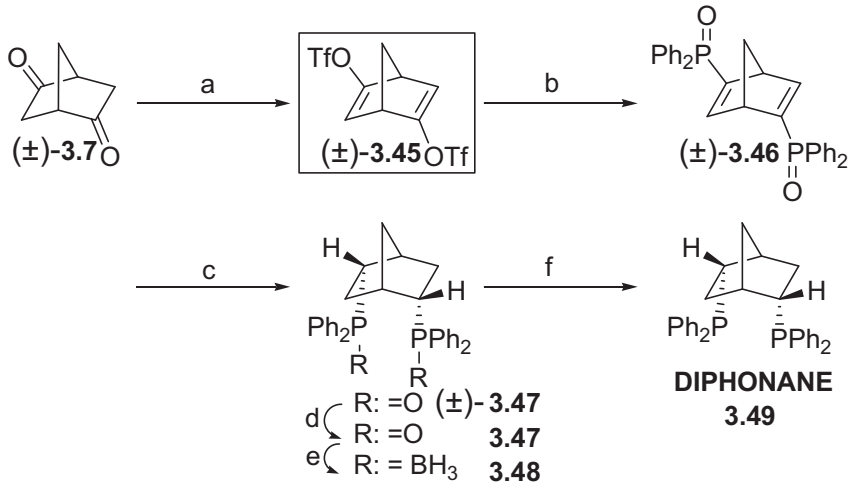
Bolm[51]

***Figure 3.7**. Literature examples of hybrid phosphane-olefin ligands.*

3.4 DEFINITION OF THE PROBLEM

As we already stated, the synthesis of Hayashi's ligand (**3.10**) had some serious drawbacks.[15] Because they were unable to synthesize the vinylic bistriflate (**3.45**), an elaborate synthesis was carried out (9 steps) (Scheme 3.3). As a result of this tedious synthesis, variation of the side chains was labour-intensive and therefore not straightforward.[17]

A solution for this problem was found in our laboratory. Vandyck found that enolization of the racemic diketone (±)-**3.7** with KHMDS at -78℃ and subsequent trapping with triflating agent $PhNTf_2$ resulted in racemic bistriflate (±)-**3.45** in good yield (Scheme 3.10).[52, 53]

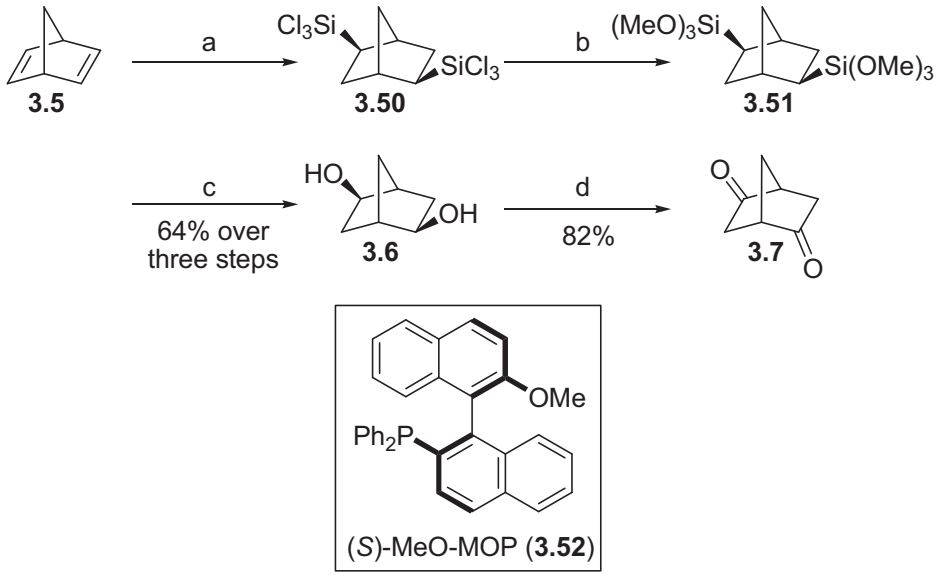


Scheme 3.10. *Synthesis of DIPHONANE (**3.49**): a) i) KHMDS, -78℃; ii) $PhNTf_2$, -78℃. b) i) $HPPh_2$, $Pd(OAc)_2$, BINAP, DIPEA, 45℃; ii) H_2O_2. c) Pd/C (10 w/w %), 4 atm H_2, MeOH. d) i) (R,R)-(2,3-di[O-(phenylamino)carbonyl]tartaric acid, EtOAc/$CHCl_3$; ii) 1M $NaHCO_3$. e) i) $HSi(OEt)_3$, $Ti(O^iPr)_4$, toluene, 100℃, 2h; ii) $BH_3.Me_2S$. f) EtOH, reflux.*

Our aim was to synthesize enantiomerically pure bistriflate **3.45** and synthesize Hayashi's ligand **3.10** along with some side chain-analogues.

3.5 SYNTHESIS OF BISTRIFLATE 3.45

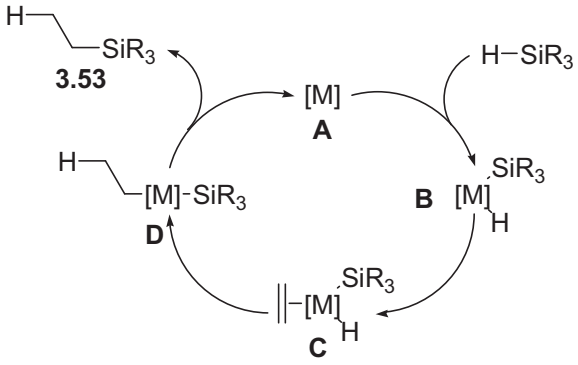
3.5.1 Synthesis of (1*S*, 4*S*)- bicyclo[2.2.1]heptane-2,5-dione (3.7)



Scheme 3.11. *Synthesis of dione (1S,4S)-(**3.7**): a) $HSiCl_3$, $[PdCl(C_3H_5)]_2$/(S)-MeO-MOP (0.1 mol % Pd), -3℃. b) MeOH, Et_3N, Et_2O. c) H_2O_2.urea, KHF_2, THF/MeOH. d) i) $(COCl)_2$, THF, -78℃, 1h; ii) Et_3N, -78℃.*

The synthesis starts with a palladium-catalyzed asymmetric hydrosilylation of bicyclo[2.2.1]heptadiene (**3.5**) with (*S*)-MeO-MOP (**3.52**) as chiral monodentate phosphane ligand.[54] If norbornadiene reacts with 1 equivalent of trichlorosilane, the monosilylated product is formed with a selectivity of 95% ee. However, when the reaction is performed with 2.5 equivalents of trichlorosilane the disilylated product (**3.50**) is formed with a higher selectivity (99% ee). This due to the double stereoselection and the fact that the minor isomer is converted to the meso product. The opposite enantiomer can be synthesized in the same way by using (*R*)- MeO-MOP.

Although high and reproducible selectivities are usually obtained, the reaction has some tedious drawbacks. The only silane that can be used is $HSiCl_3$, which is volatile (bp 33℃) and hydrolyses readily. Moreover, the chi ral ligand (*S*)-MeO-MOP (**3.52**) is very expensive. And finally, the reaction itself is very exothermic. Hence, a slow and controlled addition of norbornadiene (**3.5**) to the reaction mixture is recommended.
The most commonly accepted mechanism for the hydrosilylation was described by Chalk and Harrod (Scheme **3.12**).[55,56,57] First, oxidative addition of a hydrosilane gives a hydrido-silyl complex **B**. This intermediate coordinates with the olefin (**C**). Insertion into the M-hydride bond (**D**) and finally reductive elimination gives the hydrosilylated product (**3.53**) and regenerates the catalyst (**A**).



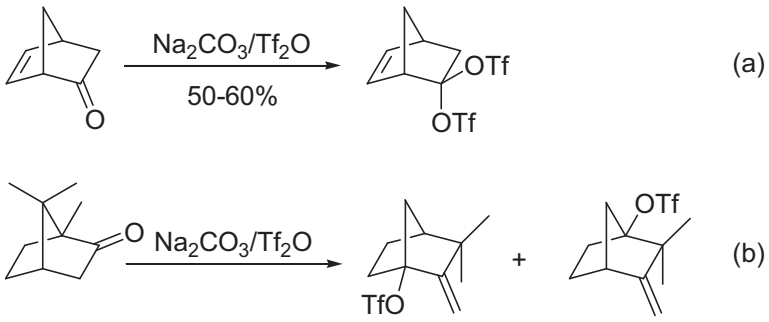
Scheme 3.12. *Chalk-Harrod mechanism for hydrosilylation*

Next, the chlorosilane **3.50** can be oxidized in one step with 30% aqueous H_2O_2 in the presence of $KF/KHCO_3$.[54c] Berkessel *et al.* mentioned that this method gave rather poor yields and suggested a two-step method.[58,59] Firstly, the chlorosilane was converted into a methyl silicate **3.51** by treatment with methanol and triethylamine. Oxidation with H_2O_2.urea in the presence of KHF_2 gave the desired alcohol **3.6**. The product was always accompanied by a small amount of meso alcohol. Via flash chromatography pure alcohol **3.6** could be obtained in 64% overall yield.

Swern oxidation of bisalcohol **3.6** nicely afforded the diketone **3.7** in 82% yield.[60]

3.5.2 Synthesis of (*S*, *S*)-bistriflate 3.45

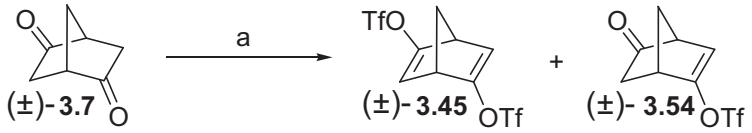
It is known that triflating of bicyclo[2.2.1]heptanone-derivatives with triflic anhydride and a base does not result in vinyltriflates but in geminal bistriflates (scheme 3.13a)[61] or rearrangement products (scheme 3.13b)[62].



Scheme 3.13. *Triflate formation with triflic anhydride and Na_2CO_3.*

In our laboratory, Vandyck *et al.* was able to synthesize racemic bistriflate (±)-**3.45** in one step from dione (±)-**3.7** in good yield (Table 3.4).[53] Crucial for a good yield were the low temperature and the use of KHMDS as a base. Hayashi *et al.* used LDA as a base for enolization and was not able to synthesize the bistriflate. Therefore, monoacetalization of the dione was necessary (scheme 3.3).[15,17] KHMDS has a pK_a of 26 in THF and is a considerably weaker base than LDA (pK_a = 36).[63,64] The use of LiHMDS afforded a comparable yield, indicating that the potassium counterion is not

really essential. Lowering the reaction temperature resulted in good yields of the bistriflate (±)-**3.45**.



	enolization	equiv	triflate formation[c]	equiv	(±)-**3.45** (%)	(±)-**3.54** (%)
1	KHMDS, 0℃, 30 min	2.2	$PhNTf_2$, 0℃, 3h	2.3	20	24
2	LiHMDS, 0℃, 15 min	2.6	$PhNTf_2$[b]	2.6	23	0
3	KHMDS, -78℃, 1h	2.6	**3.55**, -78℃, 3h	2.6	69	0
4	KHMDS, -78℃, 1h	2.6	$PhNTf_2$, -78℃, 3h	2.6	71	0
5	KHMDS, -78℃, 1h	2.1	$PhNTf_2$, -78℃, 3h	2.1	68	14

[a] ***Reagents and conditions***: i) enolization with KHMDS at indicated temperature and time; ii) trapping with triflating agent at indicated temperature and time.
[b] LiHMDS was added to a solution of diketone (±)-**3.7** and $PhNTf_2$.[65]
[c] Triflating agents:

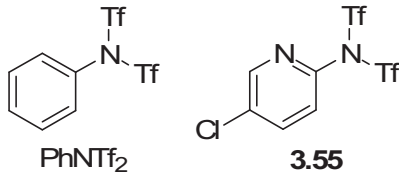
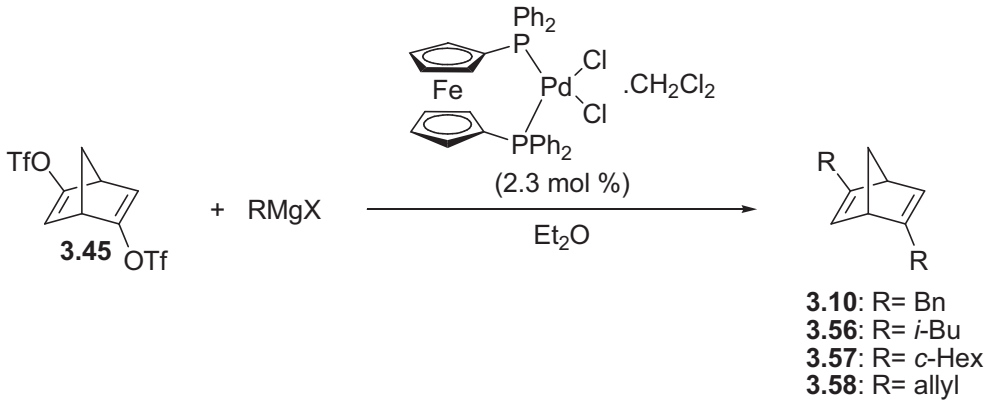


Table 3.4. *Bis-enol triflate-formation from dione* ***3.7***[a] [53]

Using the procedure as described in table 3.4 (entry 4) we could synthesize enantiomerically pure bistriflate **3.45** on a large scale (7g) in good yield (55-60% yield).

3.6 SYNTHESIS OF NORBORNADIENE LIGANDS VIA A GRIGNARD COUPLING

Introduction of the side chains succeeded via a palladium-catalyzed cross-coupling of **3.45** with Grignard reagents in the presence of $PdCl_2(dppf).CH_2Cl_2$ as a catalyst.[66,67] In general, good yields were obtained via this method (Table 3.5).

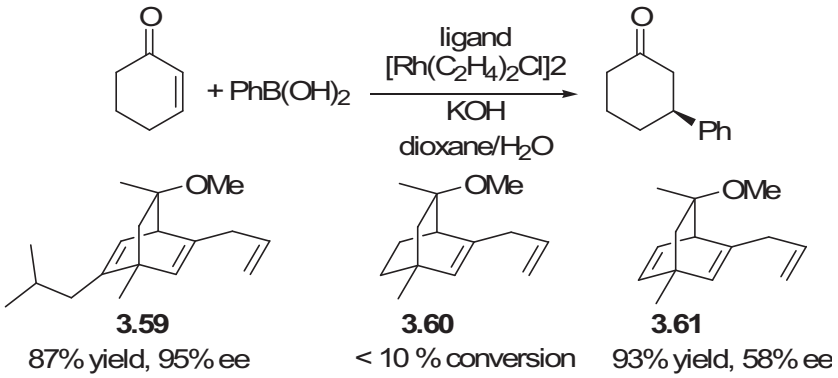


Entry	RMgX	Product	Yield (%)
1	BnMgCl (20 w/w % in THF)	(*S*, *S*)-Bn-nbd* (**3.10**)	72
2	*i*-BuMgBr (2 M in Et_2O)	(*S*, *S*)-*i*-Bu-nbd* (**3.56**)	33
3	*c*-HexMgCl (2 M in Et_2O)	(*S*, *S*)-*c*-Hex -nbd* (**3.57**)	77
4	AllylMgBr (1 M in Et_2O)	(*S*, *S*)-Allyl-nbd* (**3.58**)	41

[a] ***Reagents and conditions***: bistriflate **3.45** (1 equiv), RMgX (7 equiv), $PdCl_2(dppf).CH_2Cl_2$ (2.3 mol%), Et_2O.

Table 3.5. *Palladium(0)-catalyzed Grignard cross-coupling.*

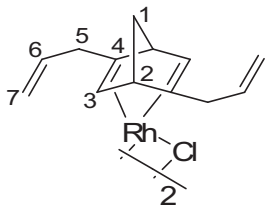
We were able to synthesize Hayashi's ligand with the benzyl side chain (**3.10)** (Table 3.5, entry 1). Cross-coupling with BnMgCl produced a significant amount of 1,2-diphenylethane via homocoupling. The latter was readily sublimed from the diene ligand under reduced pressure at room temperature.
Furthermore, we wanted to prepare more sterically demanding analogues (**3.56**: R= *i*-Bu and **3.57**: R= *c*-Hex) and one with exocyclic double bonds (**3.58**) (Table 3.5, entries 2-4). The low yields, obtained for the *i*-Bu- (**3.56**) and allyl-analogue (**3.57**), are due to the volatility of the ligands because of their low molar mass and branched structure in the absence of any functionality. The allyl analogue (**3.58**) was inspired by the work of Carreira.[19] Carreira *et al.* found that the presence of an allyl substituent resulted in an enhancement of the selectivity in the rhodium-catalyzed asymmetric 1,4-addition. A study of **3.59** by ^1H NMR indicated that all three double bonds were involved in the complexation with rhodium. They synthesized two new ligands to investigate this remarkable effect: **3.60** failed to give a significant amount of product while **3.61** gave the product in high yield but with a decreased selectivity (Scheme 3.14).



Scheme 3.14. *Effect of the introduction of exocyclic olefin moieties.*

We synthesized a rhodium complex of (*S*,*S*)-allyl-nbd* (**3.62**). Unfortunately, the complex **3.62** was an oil so no X-ray structures could be obtained. Therefore, we performed a study by ^{1}H NMR and APT towards the structure of this complex **3.62**. Surprisingly, we could only detect one type of complex. It was immediatly clear that the coordination with the rhodium metal occured via the norbornadiene double bounds (Table 3.6 and 3.7) (Figure 3.8 and 3.9). Very large high field shifts are observed for the ^{1}H and ^{13}C nuclei of the endocyclic double bonds. In the APT spectrum, we observed Rh-^{13}C coupling constants for all nuclei of the norbornadiene backbone. In sharp contrast, no coupling constants and almost no coordination shifts are noticed for the allyl substituents, indicating that these are not involved in the bonding with the metal.

Norbornadienes are highly strained bicyclic compounds. Rehybridization of the coordinated olefinic carbon center from sp^2 to sp^3 leads to a certain relief of strain. This explains why the complexation occurs exclusively with the norbornadiene double bonds.
Unfortunately, Carreira did not include the spectra of his complex, so we could not compare our spectra with his. The low conversion in the case of **3.60** suggests that the high selectivity of **3.59** is probably due to its pseudo C_2-symmetry.



3.62

Figure 3.7. *[RhCl(S,S)-allyl-nbd*]$_2$*

Chemical shift (ppm)	$\Delta\delta = (\delta_{complex} - \delta_{free\ ligand})$	assignment
1.18	- 0.77	1
2.45	- 0.49	5
2.94	0	5
3.57	+ 0.35	2
3.60	- 2.59	3
5.17	+ 0.1	7_{trans}
5.27	+ 0.1	7_{cis}
6.37	+ 0.59	6

Table 3.6. *^{1}H NMR of Rh/(S,S)-allyl-nbd* (**3.62**), coordination shift ($\Delta\delta$) and assignment.*

Chemical shift (ppm)	multiplicity	$\Delta\delta = (\delta_{complex} - \delta_{free\ ligand})$	assignment
38.47		+ 2.47	5
47.40	d, J_{C-Rh}= 10.6 Hz	- 86.11	3
53.12	d, J_{C-Rh}= 3.0 Hz	- 0.19	2
59.51	d, J_{C-Rh}= 7.5 Hz	- 12.28	1
69.41	d, J_{C-Rh}=11.3 Hz	- 87.62	4
116.62		+ 0.81	7
135.39		- 0.35	6

Table 3.7. *^{13}C NMR of Rh/(S,S)-allyl-nbd* (**3.62**), multiplicity, coordination shift ($\Delta\delta$) and assignment.*

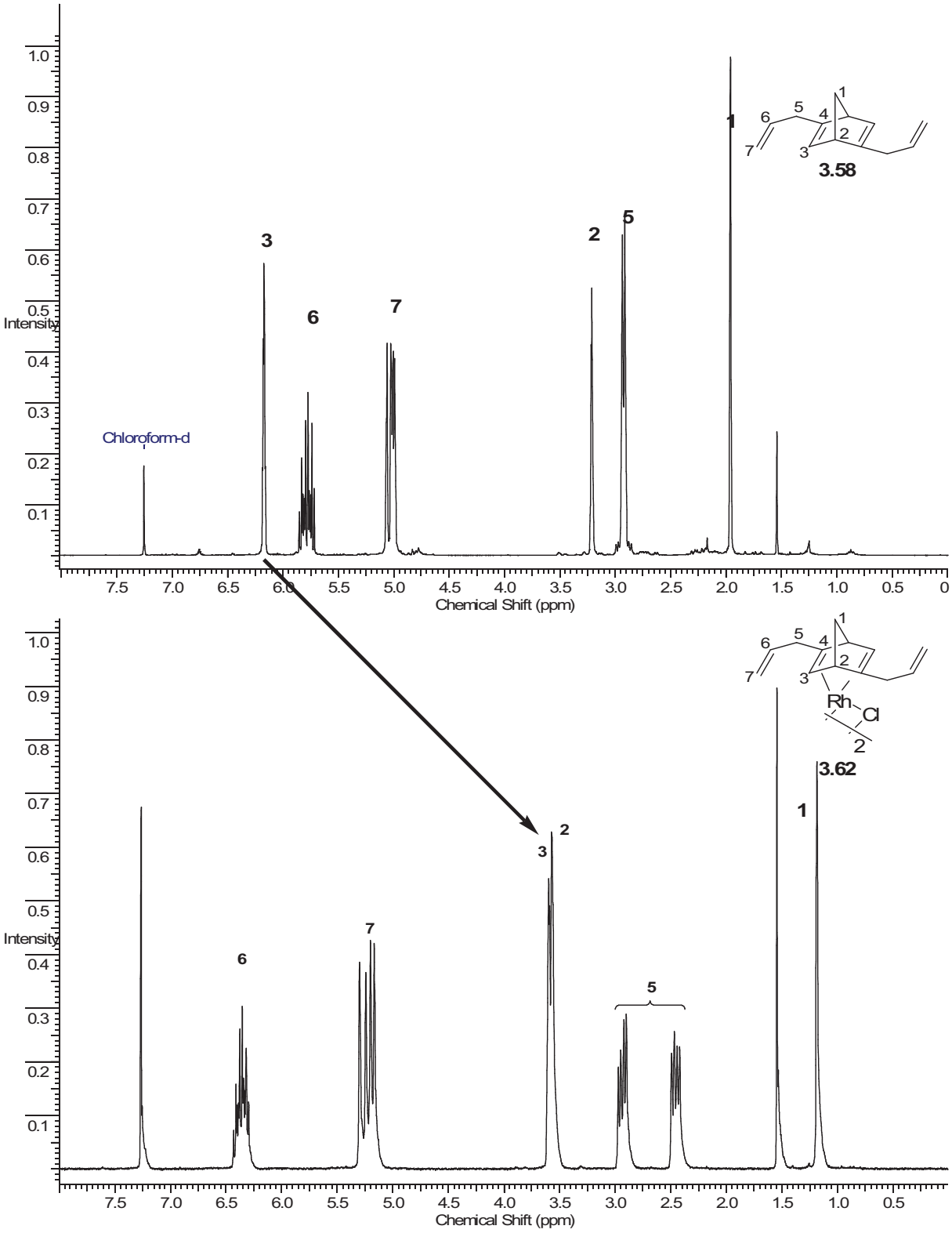


Figure 3.8. *Comparison of the ^{1}H NMR-spectra of (S,S)-allyl-nbd* (**3.58**) and $[RhCl(S,S)\text{-allyl-nbd*}]_2$ (**3.62**).*

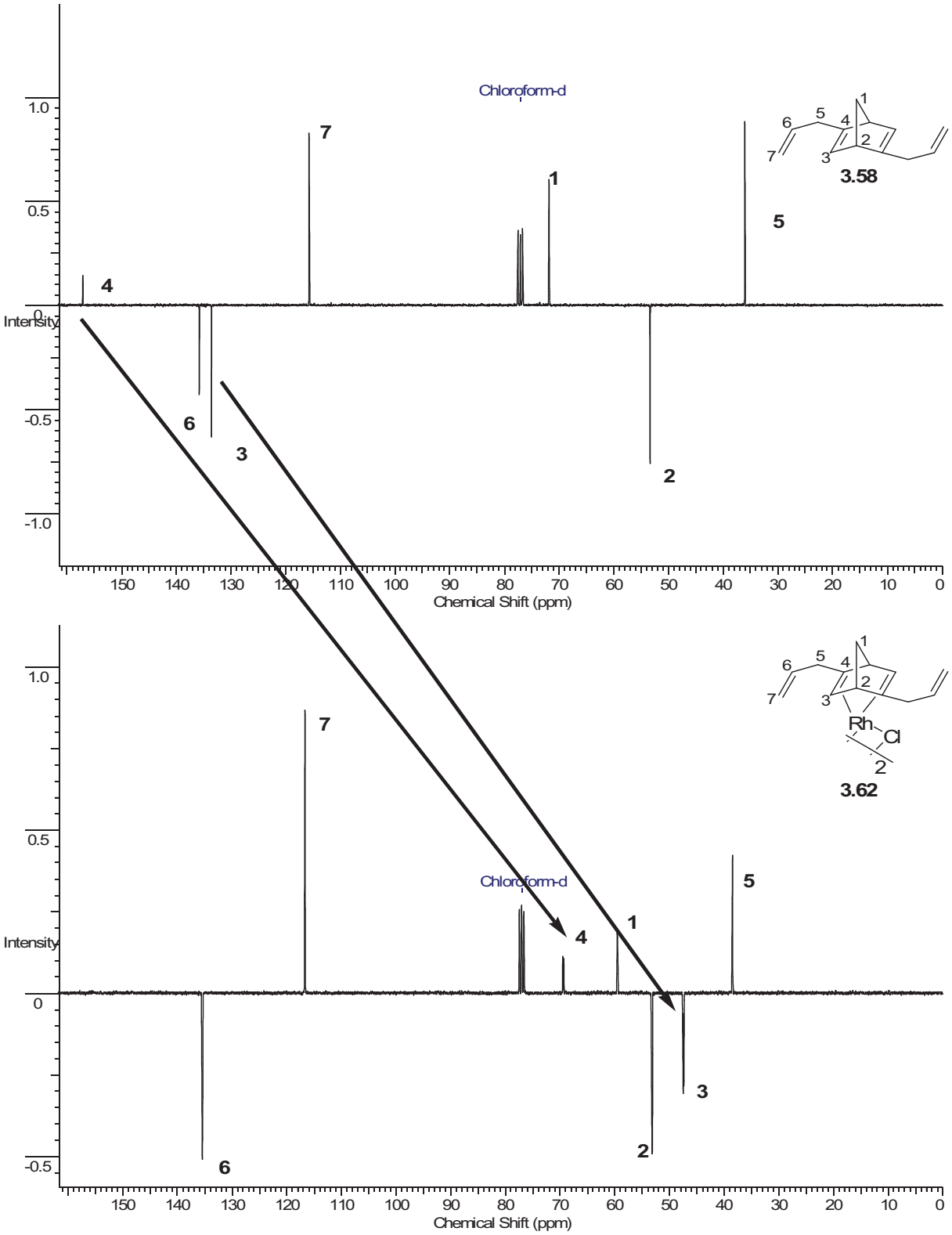
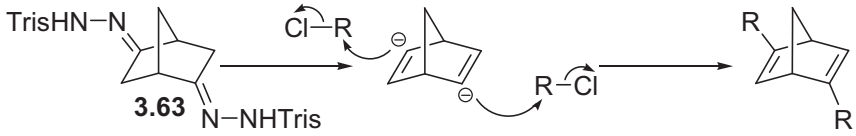


Figure 3.9. *Comparison of the ^{13}C NMR-spectra of (S,S)-allyl-nbd* (**3.58**) and [RhCl(S,S)-allyl-nbd*]$_2$ (**3.62**).*

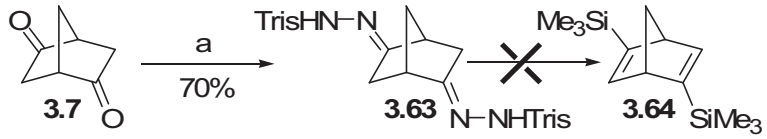
3.7 SYNTHESIS OF NORBORNADIENE LIGANDS VIA A SHAPIRO REACTION

An interesting method for preparing various norbornadiene ligands may be via a modified Shapiro reaction (Scheme 3.15).[68,69] When bis-trisylhydrazone **3.63** reacts with 2 equivalents of *n*-BuLi, a vinylic bis-carbanion is formed after decomposition at 0℃. This can then be trapped with a wide range of electrophiles to give the product alkene.[70] Via this method, it would be possible to synthesize norbornadiene ligands with silyl-substituents.[71]



Scheme 3.15. *Synthesis of dieneligands via a Shapiroreaction*

Treatment of enantiomerically pure diketone **3.7** with trisylhydrazide resulted in bis-trisylhydrazone **3.63**. We selected the trisylhydrazone instead of a tosylhydrazone because it is known that, in this way, benzylic metalation is avoided and the decomposition of the N,α-dianion to the vinyl anion is accelerated.[70]
Next, the trisylhydrazone **3.63** was subjected to a Shapiro reaction. At low temperature (-78℃), to a solution of **3.63** in THF was added 4 equivalents of *sec*-BuLi. After an hour, the orange-red solution was warmed to room temperature. Immediately, evolution of N_2 started. When N_2 evolution ceased, TMSCl was added and the resulting reaction mixture was stirred for another hour. TLC indicated a very complex mixture of products, however no sign of the desired bis-vinylsilane was observed. The use of TMEDA as a co-solvent had no beneficial effect.
The reason why we did not observe any product formation is not totally clear. Probably the dianion on a strained norbornadiene skeleton is not stable enough.



Scheme 3.16. *Synthesis of (S,S)-TMS-diene: a) trisylhydrazide (2 equiv), THF.*

However, the Shapiro reaction starting from camphor is possible.[72] Recently, (*S*,*S*)-bicyclo[3.3.1]nona-2,6-diene was synthesized via a Shapiro reaction in high yield.[73] Introduction of side chains via this method were not included.

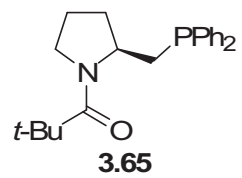
3.8 APPLICATION OF THE SYNTHESIZED CHIRAL NORBORNADIENE LIGANDS

3.8.1 Rhodium-catalyzed 1,4-additions[74]

1,4-Addition of organometallic reagents to α,β-unsaturated compounds is a very useful method for the formation of carbon-carbon bonds in organic synthesis.[75] The use of copper- and rhodium-catalyzed asymmetric 1,4-addition reactions has been most extensively studied. Copper catalysis has typically been used for the 1,4-addition of alkyl groups[76], whereas the introduction of aryl- and alkenylgroups is effected with rhodium catalysts.

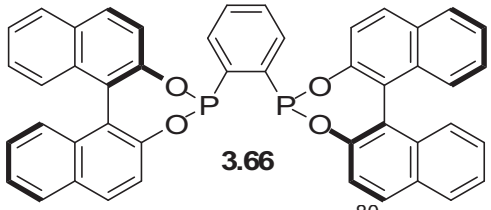
Miyaura was the first to use a rhodium catalyst for the addition of aryl- and alkenylboronic acids to several α,β-unsaturated ketones in water-containing solvents.[77] A year later, in 1998, Miyaura and Hayashi developed an efficient asymmetric variant using $Rh(acac)(C_2H_4)_2$/(*S*)-BINAP as a catalyst.[78]

Following the pioneering work of Miyaura and Hayashi, several other chiral ligands were developed for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-enones (Figure 3.10).



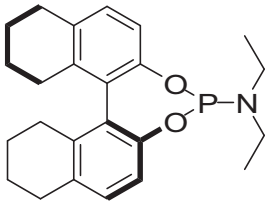
3.65

Amidomonophosphine[79]



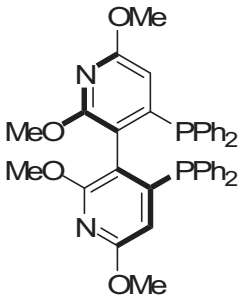
3.66

Bisphosphonite[80]

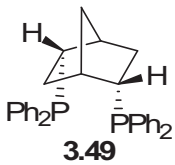


3.67

Phosphoramidite[81]

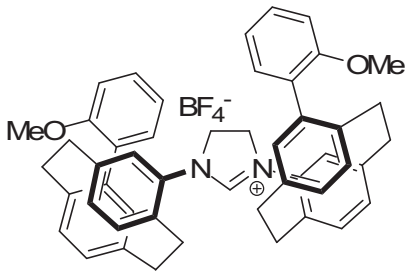


3.68



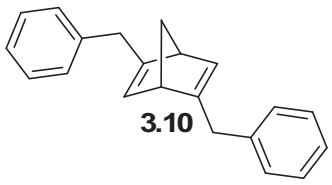
3.49

Bisphosphanes[82, 52]

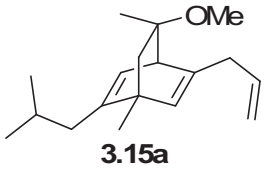


3.69

N-Heterocyclic carbene (NHC)[83]

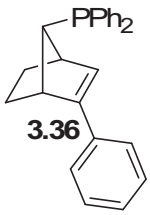


3.10



3.15a

Chiral dienes[7]



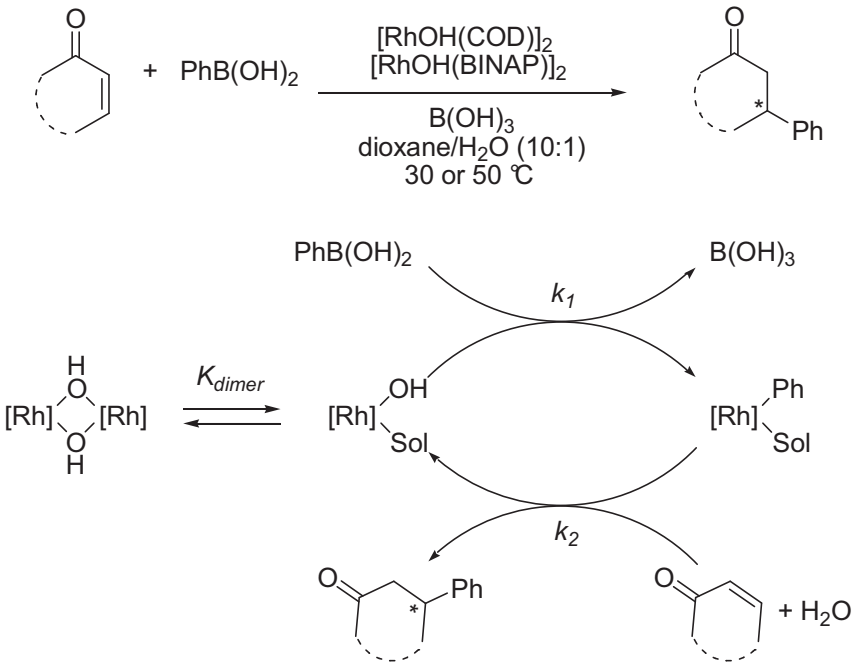
3.36

Hybrid phosphane-olefin[45]

Figure 3.10. *Chiral ligands exhibiting high enantioselectivity in the rhodium-catalyzed 1,4-addition of arylboronic acids to α,β-enones.*

As described in section 3.3, chiral dienes are excellent ligands for asymmetric conjugate additions. The high catalytic activity of diene-rhodium complexes was proven in kinetic studies by Hayashi *et al.*[84] The catalytic cycle is shown in scheme 3.17. An equilibrium (K_{dimer}) exists between a monomeric species and an inactive dimeric hydroxorhodium complex. Next, a transmetallation results in the formation of a phenylrhodium species. The transmetallation was identified as the rate-determining step. Insertion of the enone and liberation of the phenyl-adduct by addition of water regenerates the catalytically active monomeric hydroxorhodium complex. The

creation of a hydroxorhodium complex explains why the addition of bases has an accelerating effect on the 1,4-addition.[85]



Scheme 3.17. *Mechanism of the Rhodium-catalyzed 1,4-addition of phenylboronic acid to enones.*

$$v = \frac{2k_1.[PhB(OH)_2].[Rh]_{total}}{1+\sqrt{1+8K_{\dim er}.[Rh]_{total}}} \quad (1)$$

Reaction rate expression (1) was in good agreement with the reaction results. The assumption was made that $k_2.[enone]$ was much larger than $k_1.[PhB(OH)_2]$. Next, the rate and equilibrium constants could be determined by fitting the experimental data and equation 1 (Table 3.8).

	Rh/COD 30℃	Rh/COD 50℃	Rh/BINAP[86] 50℃
k_1 [M^{-1}. s^{-1}]	1.3	6.7	0.5
K_{dimer} [M^{-1}]	3.8 x 10^2	3.8 x 10^2	8 x 10^2

Table 3.8. *Rate and equilibrium constants.*

The dimerization constants do not differ much from one another. However, the rate constant k_1 for the COD complex is 13.4 times higher than for the BINAP-complex. Such a large value for the rate-determining transmetallation step (k_1) explains the high catalytic activity of diene ligands in rhodium-catalyzed 1,4-additions of $PhB(OH)_2$ to enones. Miyaura *et al.* reported a TOF of 1.0 x 10^4 h^{-1} in the 1,4-addition of an arylboronic acid with $[Rh(OH)(cod)]_2$ as a catalyst.[85] An asymmetric variant with a chiral bicyclo[2.2.2]octadiene ligand gave a TOF of 1.4 x 10^4 h^{-1} and a selectivity of 96% ee.[87] This TOF number is the highest reported for a catalytic asymmetric carbon-carbon bond-forming reaction.

The newly synthesized norbornadiene ligands (Figure 3.11) were evaluated and compared with Hayashi's ligand **3.10** in the rhodium(I)-catalyzed 1,4-addition of phenylboronic acid to cyclohexenone and cyclopentenone (Table 3.9).

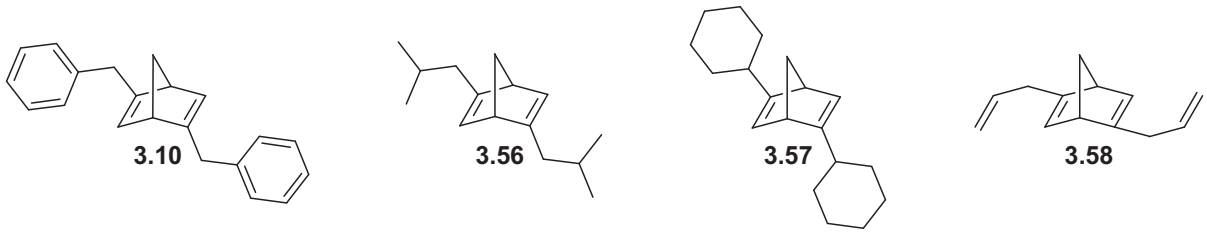
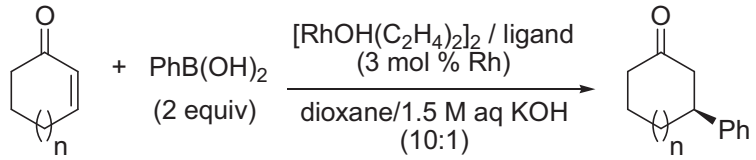


Figure 3.11. *Chiral diene ligands evaluated in the asymmetric 1,4-addition.*

The first test reaction was a verification experiment: the yield and selectivity were identical to those obtained in the original experiment of Hayashi.[15] Next, we used our new analogues (**3.56**-**3.58**). It is immediatly clear from table 3.9 that similar selectivities were obtained. An increasing sterical demand of the ligand substituents did not lead to a difference in selectivity, whereas the reaction rate was greatly influenced (Table 3.9, entries 2-3). Remarkably, the selectivity did not drop with (*S*,*S*)-allyl-nbd* (**3.58**). This again suggests that the complexation with rhodium should happen with the norbornadiene double bonds. As a result, a C_2-symmetrical complex is formed and high selectivities were obtained.

The addition to 2-cyclopentenone, a more difficult substrate, led to some surprising results. The highest selectivity was obtained with (*S*,*S*)-allyl-nbd* (**3.58**) (Table 3.9, entry 8), which is slightly better than the selectivity reported for (*R*,*R*)-Bn-nbd* (**3.10**) (Table 3.9, entry 5). The more sterically demanding (*S*,*S*)-*c*-Hex-nbd* (**3.57**) showed a considerably lower reactivity than (*S*,*S*)-*i*-Bu-nbd* (**3.56**), but, surprisingly, also a somewhat lower selectivity (Table 3.9, entries 6-7).



3.70a-b
n=1 (**a**), 0 (**b**)

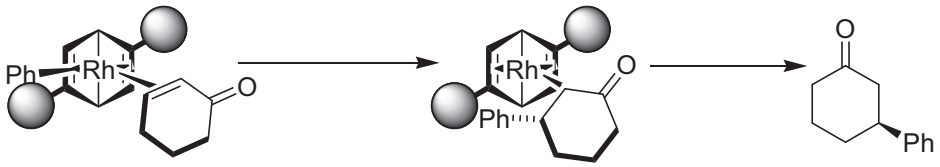
(*S*)-**3.71a-b**

Entry	substrate	Ligand	Temp (℃)	Time (h)	Yield (%)	ee (%)[b]
1	**3.70a**	**3.10**	30	1.5	95	96
2	**3.70a**	**3.56**	30	5	80	95
3	**3.70a**	**3.57**	30	16	94	95
4	**3.70a**	**3.58**	30	4.5	72	95
5[c]	**3.70b**	**3.10**	50	1	88	88
6	**3.70b**	**3.56**	25	16[d]	73	85
7	**3.70b**	**3.57**	25	16[d]	54	82
8	**3.70b**	**3.58**	25	16[d]	44	90

[a] ***Reagents and conditions:*** **3.70** (0.3 mmol), $PhB(OH)_2$ (0.6 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), ligand (ligand/Rh = 1.1/1.0), dioxane/1.5 M aq KOH(10:1).
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AS-H)
[c] Result adopted from the literature.[15]
[d] The reaction was not complete after the indicated time.

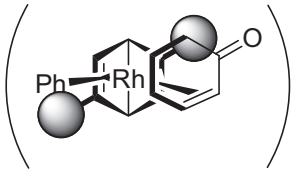
Table 3.9. *Rhodium(I)-catalyzed asymmetric 1,4-addition of $PhB(OH)_2$ to cyclic enones.*

The absolute configuration of all the products obtained with our chiral diene ligands is exclusively (*S*). With regard to the origin of stereoselectivity, the stereo-determining step is the insertion of the enone to the carbon-rhodium species coordinated with a chiral diene ligand. As shown in scheme 3.18, 2-cyclohexen-1-one (**3.70a**) should approach from the Si-face to avoid the steric hindrance of the side chain of the diene ligand. This leads to the 1,4-adduct with (*S*)-configuration, which is consistent with the observed stereochemical outcome.



si- face

(*S*)-**3.71a**



re- face

Scheme 3.18. *The stereoselectivity in the Rh(I)-catalyzed 1,4-addition with (S,S)-disubstituted-diene ligands.*

It should be noted that the mode of enantioface discrimination of diene ligands is substantially different from that of bisphosphane ligands. The creation of a chiral environment around the metal by C_2-symmetrical diene ligands is very efficient. This is due to the sterical difference between the hydrogen and the bulky substituents (Figure 3.12a). In contrast, the chiral environment of a metal/bisphosphane complex is usually controlled by the face/edge orientations of the phenyl groups on the phosphorus atoms (Figure 3.12b). The space discrimination is rigidly controlled by the size of the substituents in the case of chiral dienes. This rigid feature makes it easy to predict the stereochemical outcome of the reactions. In the case of BINAP, it is rather a conformational differentiation.

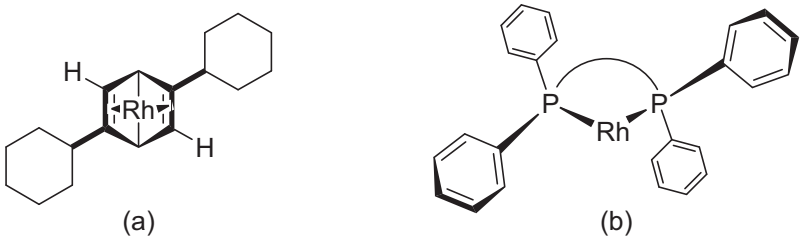
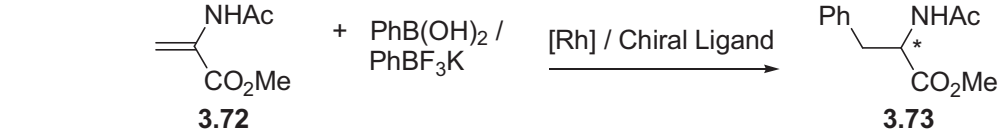
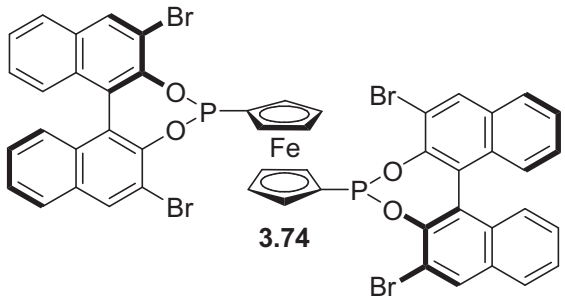


Figure 3.12. *Comparison of the creation of the chiral environment by (a) chiral (S,S)-c-Hex-nbd** (**3.57**) *and (b) (S)-BINAP.*

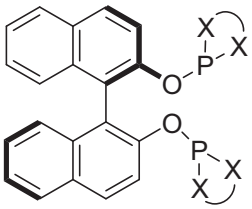
An interesting reaction is the 1,4-addition of $PhB(OH)_2$ to α-acetamido acrylic ester **3.72** giving phenylalanine derivatives **3.73** (Scheme 3.19). The stereochemistry is in this case not determined at the insertion step but at the hydrolysis step. The use of bisphosphonite **3.74** resulted in quantitative yield and a selectivity of 77% ee.[80] A bisphosphite ligand **3.75** formed the product in 91% yield and a selectivity of 72% ee.[88] The use of a BINAP/rhodium catalyst and $PhBF_3K$ resulted in 100% conversion. However, the product was racemic when water was used as a proton source. The use of guaiacol, a more-hindered proton source, proved to be crucial and a selectivity of 89.5% ee was achieved.[89] With $PhB(OH)_2$, a lower yield and selectivity was obtained (42% yield, 42% ee). This was explained by the fact that boronic acids can act as competitive proton sources.



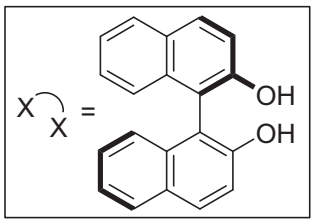
3.72 **3.73**



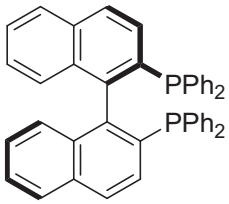
3.74



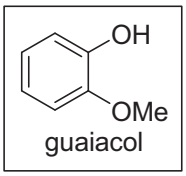
3.75



Bisphosphonite (100% yield, 77% ee) **Bisphosphite** (91% yield, 72% ee)



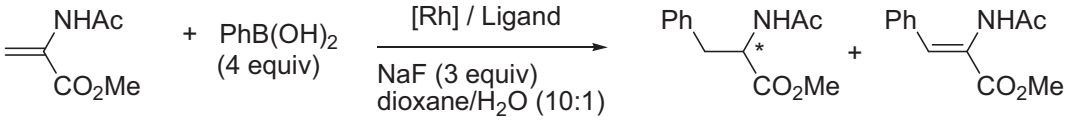
3.76



BINAP (89% yield, 89.5% ee)

Scheme 3.19. *Rhodium(I)-catalyzed asymmetric 1,4-addition to α-acetamido acrylic ester.*

We wanted to investigate if diene ligands were effective in this type of 1,4-addition. First, we tried to optimize the reaction conditions with achiral ligands (Table 3.10).



3.72 **3.73** **3.77**

	Rhodium catalyst	Additive	Temp (℃)	Time (h)	Total Yield[b] (%)	% Conjugate adduct[c] **3.73**	% Heck product[c] **3.77**
1	$[Rh(COD)Cl]_2$	/	100	24	77	82	18
2	$[Rh(COD)Cl]_2$	/	50	24	21	67	33
3	$[Rh(COD)Cl]_2$	1.5M aq KOH	50	24	23	64	36
4	$Rh(COD)(CH_3CN)_2.BF_4$	/	100	48	54	83	17
5	$[Rh(COD)OH]_2$	/	100	24	56	74	26
6	$[Rh(nbd)Cl]_2$	/	100	24	36	22	78
7	$[Rh(ethene)Cl]_2$	/	100	48	39	25	75
8	$Rh(acac)(ethene)_2$	/	100	48	34	21	79

[a] ***Reagents and conditions**:* **3.72** (0.5 mmol), $PhB(OH)_2$ (2.0 mmol), NaF (1.5 mmol), [Rh] (3 mol % Rh), dioxane/H_2O (10:1).
[b] Isolated as a mixture of 1,4-adduct and Heck product.
[c] The ratio conjugate adduct / Heck product was determined via GC on a Chiralsil-Val column.

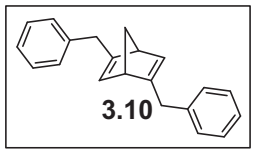
Table 3.10. *Rhodium(I)-catalyzed 1,4-addition versus Heck reaction.*

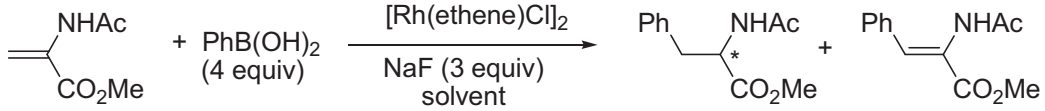
The reaction proceeded well but, to our surprise, we found that besides the conjugate addition product also a Heck-type product was formed. This was not yet reported in the literature for this substrate. Normally Heck reactions are typically catalyzed with Pd(0)-complexes.[90] Also, iridium[91]- and ruthenium[92]-catalyzed Heck reactions are described in the literature.
Lautens *et al.* were the first to describe a rhodium-catalyzed Heck-type coupling with styrenes.[93] It was attributed to the fact that styrenes are incapable of enolization. Almost at the same time, Mori *et al.* reported that it was possible to produce the Heck product with a rhodium catalyst in anhydrous THF.[94] However by a simple solvent-switch to THF/H_2O, the major product became the 1,4-adduct. The reason for this is that the intermediate oxa-π-allylrhodium is readily protonated to form the conjugate adduct and at the same time the hydroxorhodium complex is regenerated. The preference for the conjugate addition appears to improve when the substrate has a more electron-deficient carbonyl group. Methyl vinyl ketone gives exclusively the 1,4-adduct, unsaturated amides give a mixture and unsaturated esters give preferentially the Heck product. Lautens *et al.* observed that the reaction of *t*-butyl acrylate with phenylboronic acids gave preferentially the Heck product.[95] Remarkable was the fact that the solvent was toluene/H_2O. With bulky boronic acids, the conjugate product was selectively formed. The boronic acid was probably bulky enough to interfere in the Rh-H elimination. In the presence of α- or β-substituents on the acrylate, the formation of the 1,4-adduct was selective. The substituents on the acrylate may render the oxa-π-allylrhodium intermediate more basic through σ-bond inductive electron-donation and hence the protonation becomes faster.

Several reaction parameters were adjusted in order to manipulate the reaction outcome (Table 3.10, entries 2-8). A lower temperature resulted in a lower yield and

also a lower selectivity for the conjugate addition product (Table 3.10, entry 2). Addition of KOH gave a similar result (Table 3.10, entry 3). $Rh(COD)(CH_3CN)_2.BF_4$ as a catalyst resulted in a similar selectivity as the first experiment but a somewhat lower yield (Table 3.10, entry 4). With OH^- as counterion, a lower yield and a lower selectivity for 1,4-adduct was obtained (Table 3.10, entry 5). A remarkable result was obtained with norbornadiene and ethene as ligands: the selectivity was clearly in favour of the Heck product (Table 3.10, entry 6-8). So, by a proper choice of the ligand the selectivity could clearly be altered. Zou *et al.* have already demonstrated that Heck-coupling was selectively obtained in the presence of triphenylphosphane while conjugate addition was favoured in the presence of bisphosphanes.[96]

Although the selectivity for the conjugate addition was low in the presence of norbornadiene (22 % 1,4-adduct), we wanted to perform the reaction in the presence of the chiral Hayashi ligand **3.10** (Table 3.11). First, we carried out the reaction analogous to the experiment with the achiral norbornadiene. The results were similar; a slightly higher total yield was obtained (Table 3.11, entry 1). A higher selectivity for the conjugate adduct was observed but no chiral induction. The use of aq. KOH as cosolvent resulted in both a lower total and 1,4-adduct yield. A noticeable enantioselectivity was observed, albeit very low (Table 3.11, entry 2). Again, lowering the reaction temperature resulted in a lower total yield and a lower selectivity for the 1,4-adduct (Table 3.11, entry 3). Using toluene/H_2O (10:1) as a solvent-system gave a higher selectivity in favour of the 1,4-adduct. The enantioselectivity was higher although still unsatisfactory (Table 3.11, entry 4). The use of EtOH/H_2O resulted in an almost 50/50 mixture of Heck product and 1,4-adduct and a similar enantioselectivity (Table 3.11, entry 5).





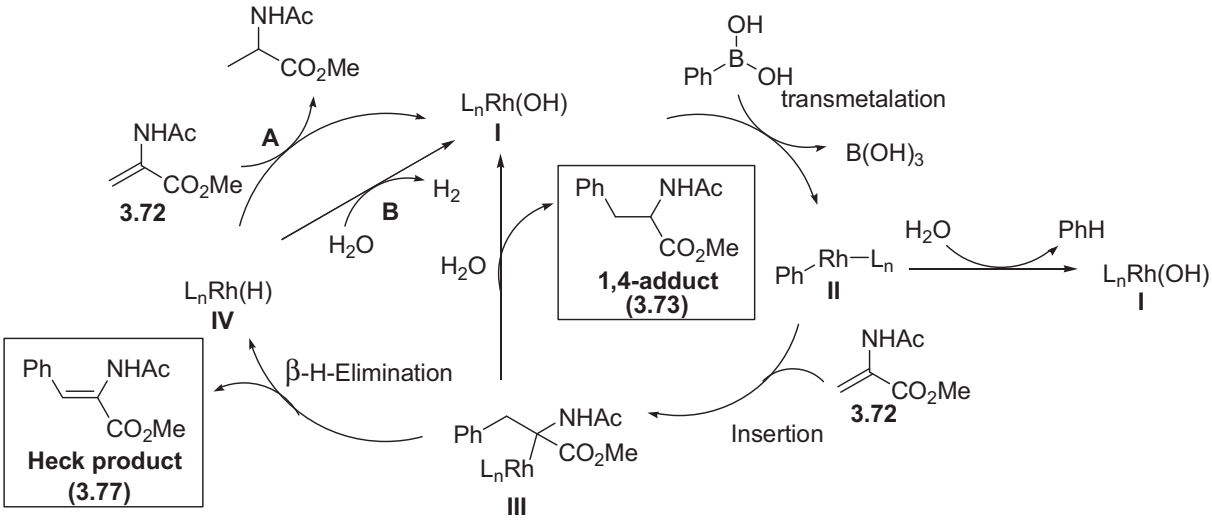
3.72 **3.73** **3.77**

Entry	Solvent	Temp (℃)	Time (h)	Total Yield[b] (%)	% Conjugate adduct (ee [%])[c]	% Heck product[c]
1	dioxane/H_2O (10:1)	100	24	40	30 (rac)	70
2	dioxane/ 1.5M aq KOH (10:1)	100	24	27	24 (9)	76
3	dioxane/H_2O (10:1)	50	48	8	27 (6)	73
4	toluene/H_2O (10:1)	50	48	12	60 (20)	40
5	EtOH/H_2O (10:1)	50	48	10	46 (21)	54

[a] ***Reagents and conditions**:* **3.72** (0.25 mmol), $PhB(OH)_2$ (1.0 mmol), NaF (0.75 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), **3.10** (**3.10**/Rh = 1.1/1.0), solvent.
[b] Isolated as a mixture of 1,4-adduct and Heck product.
[c] The ratio conjugate adduct / Heck product and enantiomeric excess was determined via GC on a Chiralsil-Val column.

Table 3.11. *Chiral diene/rhodium(I)-catalyzed 1,4-addition versus Heck reaction.*

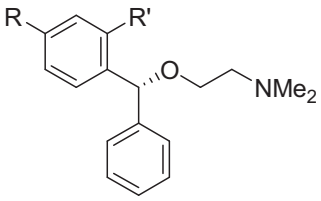
A mechanism for the observed transformations is proposed in scheme 3.20.[95] The catalytically active hydroxorhodium (**I**) transmetallates with phenylboronic acid to form the phenylrhodium species (**II**). Next, insertion of the alkene (**3.72**) results in formation in a Rh-C bond (**III**). Addition of H_2O results in the formation of the 1,4-adduct (**3.73**) and regenerates the hydroxorhodium (**I**) catalyst. A second possibility is the β-hydride elimination to generate the Heck product (**3.77**) and a rhodium hydride (**IV**). Subsequently the rhodium hydride (**IV**) should be converted into the hydroxorhodium (**I**). This can be done if we consider that the alkene (**3.72**) is used as a hydride acceptor (path **A**). Although we did not immediately discover traces of this product, it would explain the low yields obtained when the Heck product was the major product. It can also explain the lower ee's in the asymmetric reactions when the Heck product (**3.77**) is used as as hydride acceptor. A second possibility is reaction of Rh-H (**IV**) with H_2O to Rh-OH (path **B**).[97] The excess of boronic acid is partly consumed by reaction of the phenylrhodium species (**II**) with H_2O.



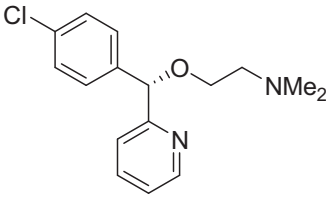
Scheme 3.20. *Proposed catalytic cycle for rhodium-catalyzed 1,4-addition versus Heck coupling.*

3.8.2 The asymmetric synthesis of diarylmethanols via a rhodium-catalyzed 1,2-addition[98,99,100]

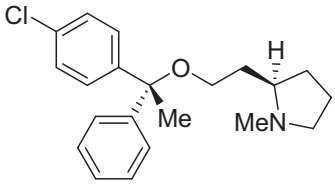
Enantiomerically pure diarylmethanols are important precursors for the synthesis of biologically active compounds, e.g. (*R*)-orphenadrine (**3.78**, an anticholinergic drug), (*R*)-neobenodine (**3.79**, an antihistamine drug), (*R*,*R*)-clemastine (**3.80**, an antihistamine drug) and (*S*)-carbinoxamine (**3.81**, an antihistamine drug) (Figure 3.13).[101]



R= Me, R'= H **3.78**
R= H, R'= Me **3.79**



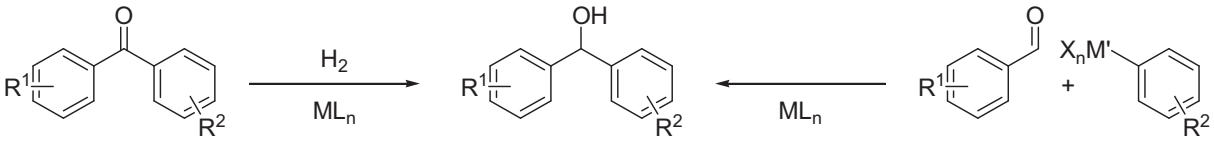
3.80



3.81

Figure 3.13. *Chiral physiologically active compounds with a diarylmethane moiety.*

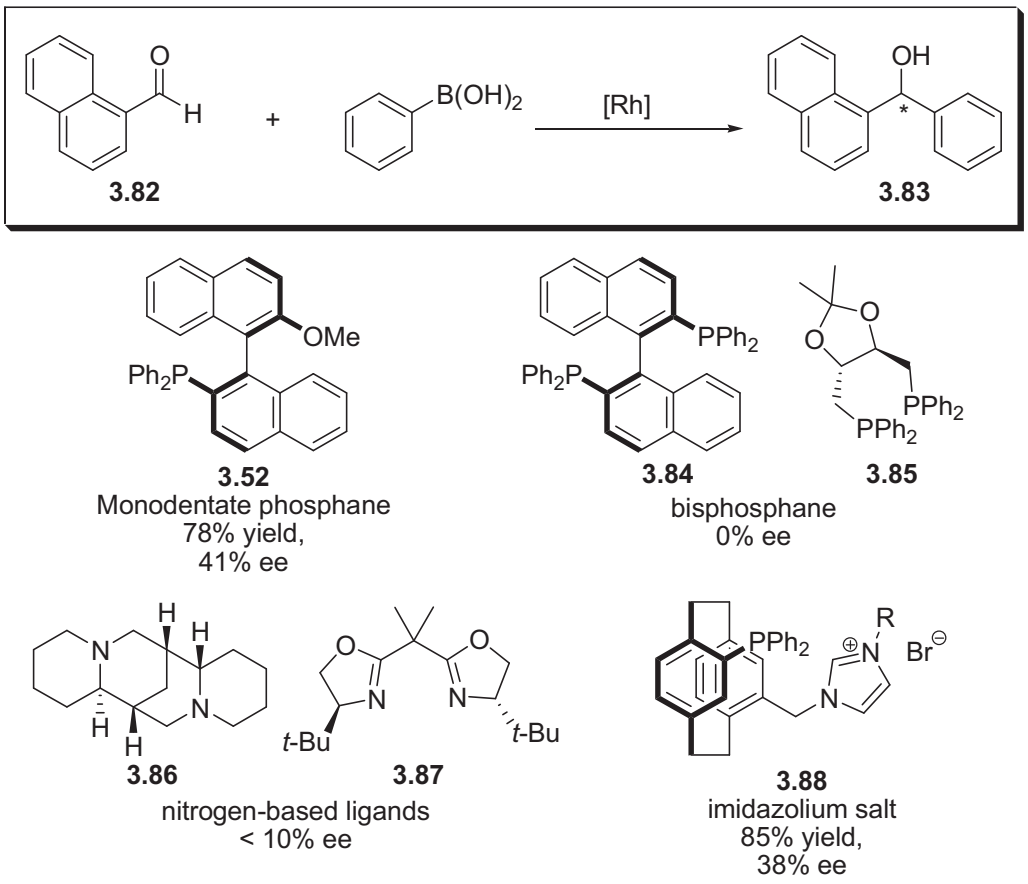
The asymmetric synthesis of diarylmethanols can be achieved via two strategies: either an asymmetric reduction of the prochiral ketones or the asymmetric addition of aryl organometallic reagents to arylaldehydes (Scheme 3.21). The reduction strategy is often very efficient and cost-effective. However, high enantioselectivities are almost exclusively obtained with *ortho*-substituted benzophenones.[102] In contrast, the asymmetric addition of aryl organometallic reagents to benzaldehydes looks more appropriate for obtaining high selectivities due to the larger difference between the phenyl and the hydrogen atom.



Scheme 3.21. *General synthetic strategies towards diarylmethanols.*

A very convenient method was developed by Bolm *et al.* using a mixture of Ph_2Zn/Et_2Zn (1:2). Several benzaldehydes were arylated with high enantioselectivies.[103] This method was further extended by mixing Et_2Zn with triphenylborane[104] or with phenylboronic acids[105].

The use of arylboronic acids as arylating agents has some important advantages over zinc reagents. They are shelf stable, readily available and compatible with a large variety of functional groups. Several groups have tried to synthesize chiral diarylmethanols via a rhodium-catalyzed 1,2-addition of phenylboronic acids to benzaldehydes (scheme 3.22). In 1998, Miyaura *et al.* reported an enantioselectivity of 41% ee with (*S*)-MeO-MOP (**3.52**) as a ligand.[106] Bidentate phosphanes such as BINAP (**3.84**) and DIOP (**3.85**) resulted in the formation of racemic alcohols. Also, chiral nitrogen-based ligands (-)-sparteine (**3.86**), bisoxazoline (**3.87**) resulted in very low selectivities.[107] Bolm *et al.* synthesized a chiral [2.2] paracyclophane-based NHC (**3.88**). However, again low selectivities were obtained.[108]



Scheme 3.22. *Literature examples for the rhodium-catalyzed 1,2-addition of phenylboronic acids to benzaldehydes.*

Given the excellent performance of chiral diene/rhodium catalysts in the asymmetric 1,2-addition of arylboronic acids to imines[7], we wanted to investigate their ability to catalyze the challenging 1,2-addition to aldehydes. In a first attempt, we tried to find optimal reaction conditions using achiral norbornadiene as a ligand. We chose this ligand because of the similarity of this catalyst with our own chiral diene ligands (Table 3.12).

Entry	Solvent	Temp (℃)	Time (h)	Yield (%)
1	dioxane/H_2O (10:1)	60	48	0
2	dioxane/1.5 M aq KOH (10:1)	60	48	32
3[b]	dioxane/1.5 M aq KOH (10:3)	50	6	78
4[c]	dioxane/1.5 M aq KOH (10:3)	50	16	50

[a] ***Reagents and conditions***: **3.89** (0.5 mmol), $PhB(OH)_2$ (1 mmol), $[Rh(nbd)Cl]_2$ (3 mol % Rh).
[b] $PhB(OH)_2$ (6 equiv) was added in portions of 2 equiv with an interval of 2h to obtain complete conversion.
[c] The rhodium/norbornadiene complex was formed *in situ* by mixing $[Rh(C_2H_4)_2Cl]_2$ and norbornadiene (norbornadiene/Rh, 1.1/1.0).

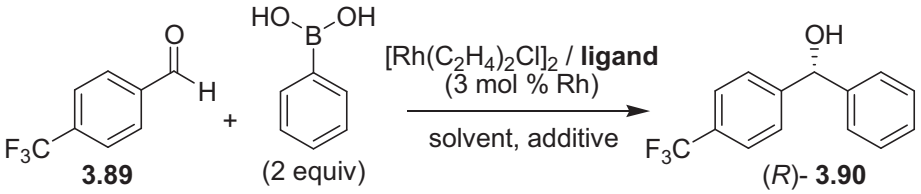
Table 3.12. *$[Rh(nbd)Cl]_2$-catalyzed 1,2-addition of $PhB(OH)_2$ to p-trifluoromethylbenzaldehyde.*[a]

In the absence of KOH, no conversion was observed (Table 3.12, entry 1) whereas in dioxane/1.5 M aq KOH (10/1) **3.90** was obtained in low yield (Table 3.12, entry 2). However, we noticed that all the $PhB(OH)_2$ was consumed due to hydrolysis. Therefore, 6 equiv of $PhB(OH)_2$ was added in portions of 2 equiv with an interval of 2h to give complete conversion in dioxane/1.5 M aq KOH (10/3) (Table 3.12, entry 3). When the catalyst was formed *in situ* a slower reaction was observed (Table 3.12, entry 4). These results indicated that the diene ligands can indeed efficiently catalyze the 1,2-addition to aldehydes.

Quite remarkably, with (S,S)-Bn-nbd* (**3.10**) as a chiral ligand (Table 3.13), the reaction was finished within 1 h, using only 2 equiv of $PhB(OH)_2$ (Table 3.13, entry 1). The reaction was highly accelerated by this catalyst, although the selectivity was only 25% ee. Changing the solvent did not improve the ee (Table 3.13, entries 2 and 3). Adding 2 equiv of KF instead of KOH did not lead to any improvement (Table 3.13, entry 4). Lowering the reaction temperature resulted in a higher selectivity up to 33% ee, while -remarkably- no loss of catalytic activity was observed (Table 3.13, entries 5 and 6). Changing the ligand showed higher selectivity and equal reactivity for (S,S)-*i*-Bu-nbd* (**3.56**) (37% ee) (Table 3.13, entry 7), while the selectivity and reactivity were considerably lower for the more bulky (S,S)-c-Hex-nbd* (**3.57**) (12% ee) (Table 3.13, entry 8). The selectivity of (S,S)-allyl-nbd* (**3.58**) was slightly lower than for (S,S)-Bn-nbd* (**3.10**) (Table 3.13, entries 9 and 6). Changing the rhodium source appeared to have a pronounced influence on the reactivity. Use of $[Rh(acac)(C_2H_4)_2]_2$ as a catalyst precursor led to a comparable enantioselectivity but a much slower reaction at room temperature in combination with **3.58** (Table 3.13, entry 10). Using $[Rh(COD)_2]BF_4.xH_2O$ as a catalyst precursor in combination with **3.58** resulted in a high yield, albeit after a considerably longer reaction time, but poor enantioselectivity (Table 3.13, entry 11).

In an attempt to further improve enantioselectivity by lowering reaction temperature to -25 ℃, a combination of dioxane and ethanol (1/1) was used (Table 3.13, entry 12), resulting in a significantly higher enantioselectivity but a slow and incomplete

reaction. Because of the apparent beneficial influence of a protic solvent on the ee, dioxane was omitted and replaced by methanol, ethanol or isopropanol at 0–25 ℃ (Table 3.13, entries 13–15). In all cases, high yields and an improved selectivity were obtained as compared to dioxane (Table 3.13, entry 7). In methanol, the reaction rate at room temperature had decreased as compared to dioxane at 0 ℃ (Table 3.13, entries 13 and 7), while for ethanol and isopropanol at 0 ℃ it was comparable (Table 3.13, entries 14 and 15). Performing the reaction in ethanol at -25 ℃ (Table 3.13, entry 16) led to the highest selectivity observed (48% ee), but a slow and incomplete reaction resulting in low yields.

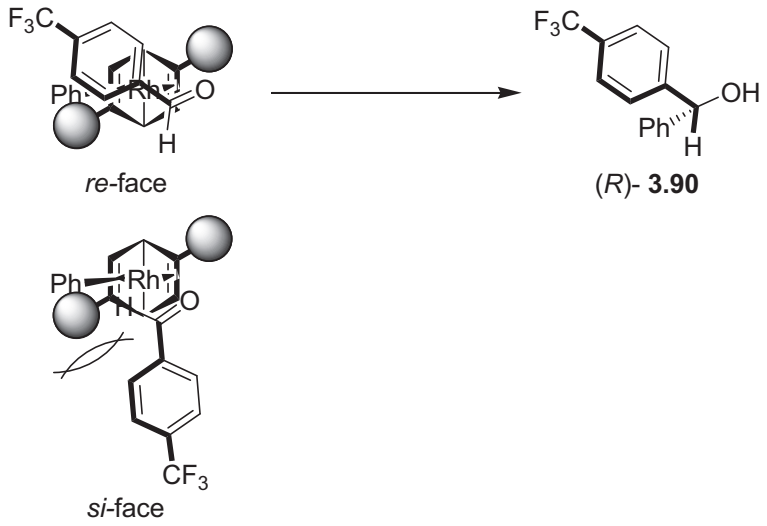


Entry	Ligand	Solvent/additive	Temp (℃)	Time (h)	Yield (%)	Ee[b] (%)
1	**3.10**	dioxane/1.5 M aq KOH (10:3)	50	1	96	25
2	**3.10**	DME/1.5 M aq KOH (10:3)	50	1	95	21
3	**3.10**	toluene/1.5 M aq KOH (10:3)	50	6	72	22
4	**3.10**	dioxane/H_2O (10:3) / KF (2 equiv)	50	3	96	25
5	**3.10**	dioxane/1.5 M aq KOH (10:3)	25	1	97	28
6	**3.10**	dioxane/1.5 M aq KOH (10:3)	0	1	95	33
7	**3.56**	dioxane/1.5 M aq KOH (10:3)	0	1	99	37
8	**3.57**	dioxane/1.5 M aq KOH (10:3)	0	16	89	12
9	**3.58**	dioxane/1.5 M aq KOH (10:3)	0	1	81	31
10[c]	**3.58**	dioxane/1.5 M aq KOH (10:3)	25	16	60	28
11[d]	**3.58**	dioxane/1.5 M aq KOH (10:3)	25	16	91	11
12	**3.56**	dioxane/EtOH/1.5 M aq KOH (5:5:3)	-25	72	23	44
13	**3.56**	MeOH/1.5 M aq KOH (10:3)	25	16	93	40
14	**3.56**	EtOH/1.5 M aq KOH (10:3)	0	3	98	41
15	**3.56**	*i*-PrOH/1.5 M aq KOH (10:3)	0	5	92	42
16	**3.56**	EtOH/1.5 M aq KOH (10:3)	-25	72	26	48

[a] ***Reagents and conditions**:* **3.89** (0.5 mmol), $PhB(OH)_2$ (1 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol% Rh), ligand (ligand/Rh = 1.1/1.0).
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OJ-H).
[c] $[Rh(acac)(C_2H_4)_2]$ was used as a rhodium source.
[d] $[Rh(COD)_2]BF_4.xH_2O$ was used as a rhodium source.

Table 3.13. *Rhodium-catalyzed asymmetric 1,2-addition of $PhB(OH)_2$ to p-trifluoromethylbenzaldehyde.*

The absolute configuration of the major enantiomer obtained with our chiral diene ligands was (*R*). The origin of stereoselectivity is analogous to the model for the 1,4-addition. In order to avoid repulsion of the aromatic ring from the substrate with the side chains of diene ligand, the substrate should approach from the *si*-face. This results in the formation of the (*R*)-enantiomer and is consistent with our observations.

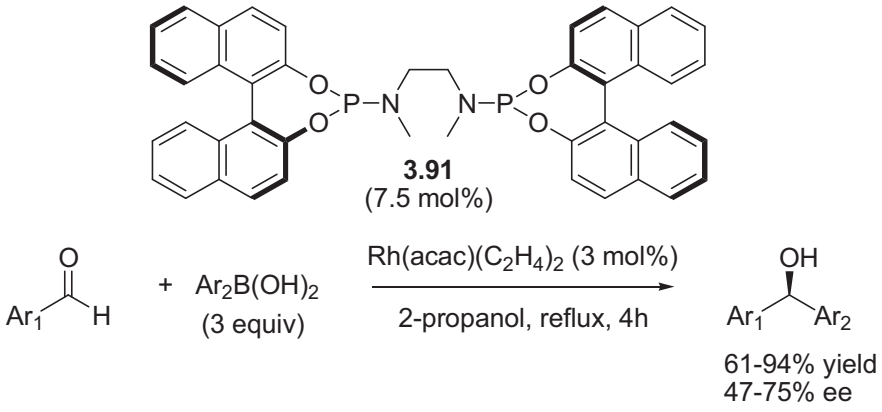


Scheme 3.23. *The stereoselectivity in the Rh(I)-catalyzed 1,2-addition with (S,S)-disubstituted-diene ligands.*

3.9 FURTHER DEVELOPMENTS

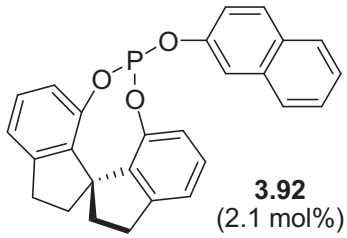
During our work, Hayashi *et al.* published a paper where he also uses the bistriflate **3.45** to synthesize analogues of **3.10**.[109] In addition, they were able to synthesize the rhodium-complexed phenyl analogue. The free ligand was previously reported to be unstable.[18] The origin of the instability is due to the presence of a styrene moiety in a strained bicyclo[2.2.1]heptadiene. This causes the lowering of the π* orbital making the compound susceptible to radical- and acid-catalyzed decomposition. This feature makes that the ligand itself is inherently unstable but it is also key for the increasing stability of the rhodium complex.

One of the main reasons why we chose to test our diene ligands in the rhodium-catalyzed asymmetric 1,2-addition of phenylboronic acids to benzaldehydes was the lack of good ligands for this transformation. While we were performing the tests, two new publications appeared on this subject. Feringa *et al.* reported that via a combinatorial approach a bidentate phosphoramidite **3.91** was selected which induced good selectivities (47-75% ee) (Scheme 3.24).[100,110]

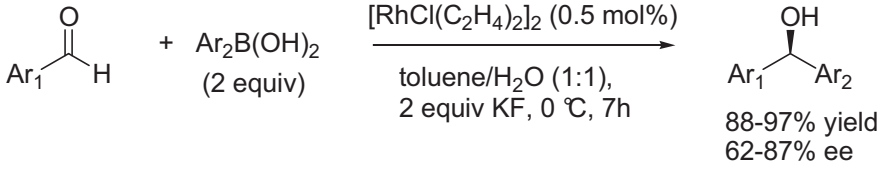


Scheme 3.24. *Feringa's bidentate phosphoramidite.*

Almost simultaneously with the publication of Feringa, Zhou *et al.* reported that spiro monophosphite **3.92** gave good yields and selectivities in this type of reaction (Scheme 3.25).[111]



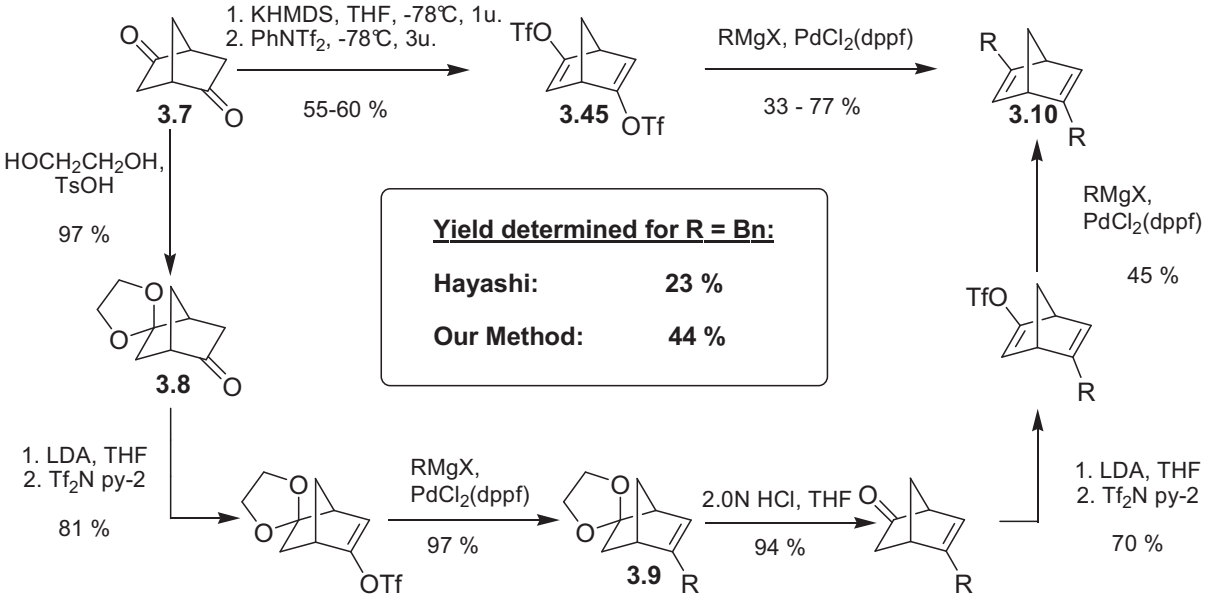
3.92
(2.1 mol%)



Scheme 3.25. *Zhou's monodentate phosphate.*

3.10 CONCLUSIONS

In summary, a novel route to synthesize chiral disubstituted bicyclo[2.2.1]heptadiene ligands was described. Advantages are a higher overall yield and the possibility of a simultaneous introduction of both substituents (Scheme 3.26).



Scheme 3.26. *Comparison of our new method and the original method of Hayashi.*

Next, the ligands were tested in several rhodium-catalyzed asymmetric test reactions. The ligands performed best in the rhodium-catalyzed asymmetric 1,4-addition to cyclic enones. Enantioselectivities up to 96% ee were obtained.

In the 1,4-addition to α-acetamido acrylic ester, the formation of a Heck-type product was observed as a side product. Moreover, the ratio of the conjugate adduct / Heck product could be adjusted by the proper choice of the ligand in the achiral version. When we turned to the asymmetric reaction with ligand **3.10** low yields and selectivities were detected.

Given the nice results of chiral diene/rhodium complexes in 1,4-additions to cyclic enones, we investigated the rhodium-catalyzed 1,2-addition of phenylboronic acids to benzaldehydes. This reaction can be considered as a challenging reaction. The presence of the alkyl side chains on the ligand appeared to be crucial for the catalytic effect, resulting in a dramatically higher reactivity as compared to unsubstituted norbornadiene as a ligand. On the other hand, enantioselectivities could be improved from poor to fair with ligand **3.56** (up to 48% ee).

In conclusion, chiral dienes can be used as highly selective ligands for asymmetric transition metal catalysis. However, till now they have been used almost exclusively in rhodium- and iridium-catalyzed reactions. Future work should be directed to the search of new metals compatible with these diene ligands. As a result, new reactions can be addressed.

Part of this chapter has been published: Noël, T.; Vandyck, K.; Van der Eycken, J., "*Some new C_2-symmetric bicyclo[2.2.1]heptadiene ligands: synthesis and catalytic activity in rhodium(I)-catalyzed asymmetric 1,4- and 1,2-additions"* , *Tetrahedron* **2007**, *63*, 12961-12967.

3.11 REFERENCES

[1] Hunt, L.B. *Platinum Metals Rev.* **1984**, *2*, 76-83.

[2] Johnson, J.B.; Rovis, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 840-871.

[3] Amatore, A.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178-180*, 511-528.

[4] (a) Itami, K.; Mitsudo, K.; Nishino, A.; Yoshida, J.-I. *J. Org. Chem.* **2002**, *67*, 2645-2652. (b) Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073-1076.

[5] Cope, A.C.; Ganellin, C. R.; Johnson, H.W. *J. Am. Chem. Soc.* **1962**, *84*, 3191-3192.

[6] Crabtree, R.H. In *The Organometallic Chemistry of the Transition Metals*; Wiley, 1988; pp 89-120.

[7] Defieber, C.; Grützmacher, H.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4482-4502.

[8] Mingos, D.M.P. *J. Organomet. Chem.* **2001**, *635*, 1-8.

[9] Dapprich, S.; Frenking, G. *J. Phys. Chem.* **1995**, *99*, 9352-9362.

[10] Ziegler, T.; Rauk, A. *Inorg. Chem.* **1979**, *18*, 1558-1565.

[11] (a) Frenking, G. *J. Organomet. Chem.* **2001**, *635*, 9-23. (b) Massera, C.; Frenking, G. *Organometallics* **2003**, *22*, 2758-2765.

[12] Frison, G.; Grützmacher, H. *J. Organomet. Chem.* **2002**, *643-644*, 285-291.

[13] For a concise review: Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3364-3366.

[14] Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *J. Am. Chem. Soc.* **1998**, *120*, 1441-1446.

[15] Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.

[16] Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.

[17] Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425-3427.

[18] Tokunaga, N.; Otomaru, Y.; Okamoto,K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584-13585.

[19] Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E.M. *Org. Lett.* **2004**, *6*, 3873-3876.

[20] Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307-310.

[21] Otomaru, Y.; Okamoto,K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503-2508.

[22] Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673-1679.

[23] Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889-5892.

[24] Läng, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997-3007.

[25] Grundl, M.A.; Kennedy-Smith, J.J.; Trauner, D. *Organometallics* **2005**, *24*, 2831-2833.

[26] Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336-5337.

[27] Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331-2337.

[28] Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 860-861.

[29] Nishimura, T.; Yasuhara, Y.; Nagaosa, M.; Hayashi, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1778-1783.

[30] Okamoto,K.; Hayashi, T.; Rawal, V.H. *Org. Lett.* **2008**, *10*, 4387-4389.

[31] Hayashi, T.; Yamamoto, Y.; Tokunaga, N. *Angew. Chem. Int. Ed.* **2005**, *44*, 4224-4227.

[32] Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628-5629.

[33] Paquin, J.-F.; Stephenson, C.R.J.; Defieber, C.; Carreira, E.M. *Org. Lett.* **2005**, *7*, 3821-3824.

[34] Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2005**, 3213-3214.

[35] Shintani, R.; Okamoto,K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 4757-4759.

[36] Tokunaga, N.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 513-516.

[37] Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589-592.

[38] Tietze, L.F. *Chem. Rev.* **1996**, *96*, 115-136.

[39] Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217-224.

[40] Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54-55.

[41] Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3909-3912.

[42] Shintani, R.; Sannohe, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 7277-7280.

[43] Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1294-1295.

[44] Nishimura, T.; Yasuhara, Y.; Nagaosa, M.; Hayashi, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1778-1783.

[45] (a) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130-2138. (b) Shintani, R.; Duan, W.-L.; Okamoto, K.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 3400-3405. (c) Shintani, R.; Duan, W.-L.; Nagano, T.; Okado, A.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4611-4614.

[46] Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem. Eur. J.* **2004**, *10*, 4198-4205.

[47] Piras, E.; Läng, F.; Rüegger, H.; Stein, D.; Wörle, M.; Grützmacher, H. *Chem. Eur. J.* **2006**, *12*, 5849-5858.

[48] Kasák, P.; Arion, V.B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084-9090.

[49] Štěpnička, P.; Císařová, I. *Inorg. Chem.* **2006**, *45*, 8785-8798.

[50] Defieber, C.; Ariger, M.A.; Moriel, P.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3139-313.

[51] (a) Stemmler, R.T.; Bolm, C. *Synlett* **2007**, 1365-1370. (b) Stemmler, R.T. In Rhodium-katalysierte, asymmetrische Synthese: Ligandendesign und Methodik, Ph.D. thesis, RWTH Aachen, **2007**.

[52] Vandyck, K.; Matthys, B.; Willen, M.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Org. Lett.* **2006**, *8*, 363-366.

[53] Vandyck, K. In *Synthese en toepassing van rigide C_2-symmetrische bidentaat liganden*, Ph.D. thesis, Universiteit Gent, **2006**.

[54] (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887-9888. (b) Uozumi, Y.; Lee, S.-Y.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 7185-7188. (c) Hayashi, T.; Uozumi, Y. *Pure & Appl. Chem.* **1992**, *64*, 1911-1916. (d) Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259-266. (e) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354-362.

[55] Chalk, A.J.; Harrod, J.F. *J. Am. Chem. Soc.* **1965**, *87*, 16-21.

[56] Hayashi, T. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol. 2, pp 319-333.

[57] Berthon-Gelloz, G. In *The hydrosilylation of alkenes and alkynes catalyzed by N-heterocyclic carbene Platinum(0) complexes,* Ph.D. thesis, Université Catholique de Louvain, **2007**.

[58] Berkessel, A.; Schröder, M.; Sklorz, C.A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J. *J. Org. Chem.* **2004**, *69*, 3050-3056.

[59] Jones, G.R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599-7662.

[60] (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660. (b) Mancuso, A.J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.

[61] Martinez, A. G.; Rios, E. E.; Vilar, E. T. *Synthesis* **1979**, 382-383.

[62] Bentz, H.; Subramanian, L.R.; Hanack, M.; Martinez, A. G.; Marin, M.G.; Perez-Ossorio, R. *Tetrahedron Lett.* **1977**, 9-12.

[63] Fraser, R.R.; Mansour,T.S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232-3234.

[64] The use of KHMDS/LiHMDS was essential in the alkylation of cyanohydrin acetonides with allyl chloride: Rychnovsky, S.D.; Swenson, S.S. *J. Org. Chem.* **1997**, *62*, 1333-1340.

[65] Yamada, S.; Karasawa, S.; Takahashi, Y.; Aso, M.; Suemune, H. *Tetrahedron* **1998**, *54*, 15555-15566.

[66] Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, Y.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158-163.

[67] van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Reek, J.N.H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741-2769.

[68] Shapiro, R.H.; Heath, M.J. *J. Am. Chem. Soc.* **1967**, *89*, 5734-5735.

[69] Adlington, R.M.; Barrett, A.G.M. *Acc. Chem. Res.* **1983**, *16*, 55-59.

[70] Chamberlin, A.R.; Stemke, J.E.; Bond, F.T. *J. Org. Chem.* **1978**, *43*, 147-154.

[71] Taylor, R.T.; Degenhardt, C.R.; Melega, W.P.; Paquette, L.A. *Tetrahedron Lett.* **1977**, 159-162.

[72] (a) Traas, P.C; Boelens, H.; Takken, H.J. *Tetrahedron Lett.* **1976**, 2287-2288. (b) Taylor, R.T.; Degenhardt, C.R.; Melega, W.P.; Paquette, L.A. *Tetrahedron Lett.* **1977**, 159-162. (c) Meuzelaar, G.J.; Blom, A.; Maat, L.; Sheldon, R.A. *Eur. J. Org. Chem.* **1999**, 519-522. (d) White, T.D.; West, F.G. *Tetrahedron: Lett.* **2005**, *46*, 5629-5632.

[73] Mayr, M.; Bataille, C.J.R.; Gosiewska, S.; Raskatov, J.A.; Brown, J.M. *Tetrahedron: Asymmetry* **2008**, *19*, 1328-1332.

[74] (a) Hayashi, T. *Synlett* **2001**, 879-887. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169-196. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829-2844. (d) Shintani, R. ; Hayashi, T. In *New Frontiers In Asymmetric Catalysis*, Mikami, K.; Lautens, M., Eds.; Wley, 2007; pp 59-100.

[75] (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol. 3, 1105-1120. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol. 3, 1121-1142.

[76] (a) Feringa, B.L. *Acc. Chem. Res.* **2000**, *33*, 346-353. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236.

[77] Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229-4231.

[78] Takaya, Y.; Takahashi, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580

[79] Kuriyama, M.; Nagai, K.; Yamada, K.-i.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932-8939.

[80] Reetz, M.T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083-4085.

[81] (a) Boiteau, J.-G.; Minnaard, A.J.; Feringa, B.L. *J. Org. Chem.* **2003**, *68*, 9481-9484. (b) Boiteau, J.-G.; Imbos, R.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* **2003**, *5*, 681-684.

[82] Shi, Q.; Xu, L.; Li, X.; Jia, X.; Wang, R.; Au-Yeung, T.T.-L.; Chan, A.S.C.; Hayashi, T.; Cao, R.; Hong, M. *Tetrahedron Lett.* **2003**, *44*, 6505-6508.

[83] Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M.B. *Angew. Chem. Int. Ed.* **2003**, *42*, 5871-5874.

[84] Kina, A.; Yasuhara, Y.; Nishimura, T.; Iwamura, H.; Hayashi, T. *Chem. Asian J.* **2006**, *1*, 707-711.

[85] Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000-6004.

[86] Kina, A.; Iwamura, H.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 3904-3905.

[87] Chen, F.-X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341-344.

[88] Chapman, C.J.; Wadsworth, K.J.; Frost, C.G. *J. Organomet. Chem.* **2003**, *680*, 206-211.

[89] Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2004**, *43*, 719-723.

[90] For palladium-catalyzed Heck-type reaction of boronic acids: Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H.F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313-3316.

[91] Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 89-92.

[92] Farrington, E.J.; Brown, J.M.; Barnard, C.F.J.; Rowsell, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 169-171.

[93] Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358-5359.

[94] Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakad, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774-10775.

[95] Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, 2006-2014.

[96] Zou, G.; Guo, J.; Wang, Z.; Huang, W.; Tang, J. *Dalton Trans.* **2007**, *28*, 3055-3064.

[97] (a) Yoshida, T.; Okano, T.; Ueda, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1981**, *103*, 3411-3422. (b) Herrmann, W.A.; Kulpe, J.A.; Kellner, J.; Riepl, H.; Bahrmann, H.; Konkol, W. *Angew. Chem. Int. Ed.* **1990**, *29*, 391-393.

[98] Schmidt, F; Stemmler, R.T.; Rudolph, J.; Bolm. C. *Chem. Soc. Rev.* **2006**, *35*, 454-470.

[99] Bolm, C.; Hildebrand, J.P.; Muñiz, K.; Hermanns, N. *Angew. Chem. Int. Ed.* **2001**, *40*, 3284-3308.

[100] Jagt, R.B.C. In *Rhodium-catalyzed boronic acid additions – A combinatorial approach to homogeneous asymmetric catalysis*, Ph.D. thesis, University of Groningen, **2006**.

[101] Harms, A.F.; Hespe, W.; Nauta, W.T.; Rekker, R.F., Timmerman, H.; de Vries, J. *Drug Design* **1976**, *6*, 1-80.

[102] (a) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659- 662. (b) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40-73.

[103] (a) Bolm, C.; Hermanns, N.; Hildebrand, J.P.; Muñiz, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3465-3467. (b) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem. Int. Ed.* **2003**, *42*, 3002-3005.

[104] Rudolph, J.; Schmidt, F; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867-872.

[105] Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850-14851. (b) Schmidt, F; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 703-708.

[106] Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 3279-3281.

[107] Moreau, C.; Hague, C.; Weller, A.S.; Frost, C.G. *Tetrahedron Lett*. **2001**, *42*, 6957-6960.

[108] Focken, T.; Rudolph, J.; Bolm, C. *Synthesis* **2005**, 429-436.

[109] Berthon-Gelloz, G.; Hayashi, T. *J. Org. Chem.* **2006**, *71*, 8957-8960.

[110] Jagt, R.B.C.; Toullec, P.Y.; de Vries, J.G.; Feringa, B.L.; Minnaard, A.J. *Org. Biomol. Chem.* **2006**, *4*, 773-775.

[111] Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1479-1481.

4

CHIRAL IMIDATE LIGANDS

4.1 INTRODUCTION

In asymmetric catalysis, the most widely-used ligands are phosphane ligands. However, nitrogen-containing ligands have several distinct advantages.[1,2] First, they are largely available in enantiomerically pure form from the chiral pool. In addition, the production of chiral amines from the resolution of racemates is probably one of the easiest methods of enantiomer separation. In contrast to chiral phosphanes, chiral nitrogen atoms are difficult to obtain because of instantaneous epimerization at room temperature. The formation of a stable chiral center on a nitrogen is however, possible by using bicyclic structures, e.g. quinine (**4.1**), cinchonine (**4.2**) and sparteine (**4.3**) (Figure 4.1).

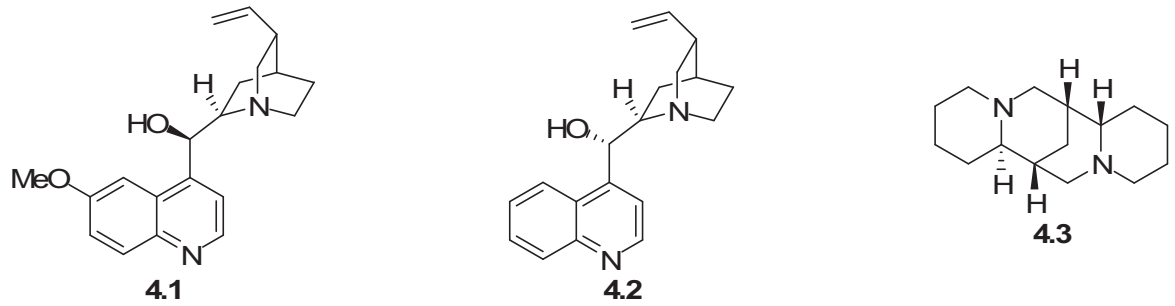


Figure 4.1. *Ligands containing chiral nitrogen atoms.*

Nitrogen-containing ligands may be used in asymmetric catalysis with other transition metals, less expensive than noble metals, e.g. cobalt complexes.[3] And they turn out to be suitable for heterogeneous catalysis which is one of their main advantages over phosphane ligands.[4]

4.2 THE METAL-NITROGEN BONDING[5,6]

Like phosphanes, nitrogen-donors have a lone pair on the central atom which can be donated to a metal. In contrast to nitrogen-donors, phosphanes are also π acceptors. The π-bond is formed between the σ* orbital of the P-R bond and a filled d orbital of the metal (Figure 4.2). Nevertheless, π interactions are possible with ligands containing sp^2-hybridized nitrogen donors.

Figure 4.2. *Coordination model with a metal for nitrogen and phosphane ligands.*

In table 4.1, M-L bond energies are listed. The results indicate that M-C bonds are weaker than the M-N bonds, which in turn are weaker than the M-O bonds.

	ML_4			$X-M^+$			
L	Ti	Zr	Hf	M	H	CH_3	NH_2
CH_2*t*-Bu	188	227	224	Sc	57(2)	59(3)	85(2)
NEt_2	309	340	367	Ti	54(3)	54(2)	85(3)
O*i*-Pr	444	518	534	V	48(2)	50(2)	73(2)
F	586	648	665	Fe	50(2)	58(2)	67(12)
				Co	47(2)	49(4)	62(2)
				Ni	40(2)	45(2)	56(5)

Table 4.1. *Mean M-L bond dissociation enthalpies [kJ.mol^{-1}] for homoleptic complexes ML_4 and M-X bond dissociation enthalpies for X= H, C, N [kcal.mol^{-1}].*

Particularly relevant for the transfer of stereospecific information from a complex to a substrate is the stability of the ligand metal complex. In table 4.2, the dissociation rate constants for mono- and bidentate nitrogen heterocycles from Ni^{II} and Co^{II} complexes are listed.[7] It is immediately clear that the monodentate ligand pyridine is much more labile than bidentate ligands, such as 2,2'-bipyridine and phenanthroline. Phenanthroline, which is a rigid ligand, is less labile than the more flexible 2,2'-bipyridine.

complex	M = Ni	M = Co
$[M(H_2O)_5(pyridine)]^{2+}$	40	8×10^{-2}
$[M(H_2O)_4(2,2'\text{-bipyridine})]^{2+}$	5×10^{-5}	6×10^{-2}
$[M(H_2O)(phenanthroline)]^{2+}$	1×10^{-5}	1×10^{-2}

Table 4.2. *Rate constants [s^{-1}] for the dissociation of mono- and bidentate nitrogen heterocycles from Ni^{II} and Co^{II} complexes: T= 25℃, pH ≈ 6.0.*

The stability of metal-ligand bonds must take into account sterical interactions. These have been successfully parametrized for P-donors with Tolman's cone angle concept (Table 4.3).[8] The cone angles (θ_P) are obtained by taking a space-filling model of the $M(PR_3)$ group, folding back the R substituents away from the metal, and measuring the angle of a cone that will just contain all of the ligand while the apex of the cone is at the metal (Figure 4.3). The corresponding values for nitrogen donors (θ_N) have also been reported (Table 4.3).[9] The cone angle for N-donors is in general larger than for the corresponding P-donors. Moreover, the difference between the two becomes greater for the larger ligands. This indicates that the strength of M-N bonds will be affected much more by sterical effects than that of the corresponding M-P bonds.

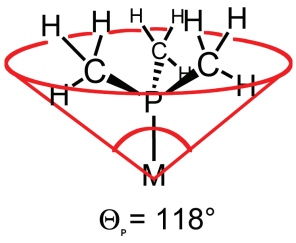


Figure 4.3. *Tolman's cone angle concept.*

Ligand	θ_P [°]	θ_N [°]
XH_3	87	94
XMe_3	118	132
XEt_3	132	150
XPh_3	145	166

Table 4.3. *Tolman's cone angle values for P-donors (θ_P) and the corresponding N-donors (θ_N).*

An important difference between phosphane and nitrogen ligands is their *trans*-effect. The *trans*-effect can be defined as the effect of a ligand upon the rate of ligand replacement of the group trans to itself.[10] As can be seen from table 4.4, phosphane ligands exert a very large labilizing effect of a *trans* positioned ligand. In sharp contrast, nitrogen donors are very weak.

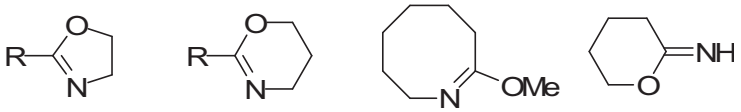
trans-effect	Donor ligand	$k_{rel.}$
very large	CO, CH^-, **C_2H_4**, **PR_3**	ca. 10^5
large	$SC(NH_2)_2$, NO_2^-, I^-, SCN^-, CH_3^-, $C_6H_5^-$	ca. 10^2
moderate	Br^-, Cl^-	ca. 1
weak	**pyridine, NH_3**, OH^-	ca. 10^{-1}

Table 4.4. *Common donors arranged in order of decreasing trans-effect and approximate values of the exchange rates of the trans ligands in a Pt^{II} complex.*

4.3 IMIDATES[11,12,13]

Imidates (**4.4**) are esters of the hypothetical imidic acids or iso-amides (**4.5**).[14] Cyclic imidates can be divided in three groups: (1) the imidate function lies completely within the ring, e.g. oxazolines (**4.6**) and dihydro-oxazines (**4.7**); (2) the oxygen function has an exocyclic position (**4.8**); (3) the imino-nitrogen has an exocyclic position (**4.9**).

4.4 **4.5**



4.6 **4.7** **4.8** **4.9**

The nitrogen analogue of imidates is the amidine group. In comparison to amidines, imidates have a smaller dipole moment. This shows that conjugation in the imidate group is less pronounced than in the case of amidines. However, the conjugation favours a planar arrangement of the imidate group (Figure 4.4).

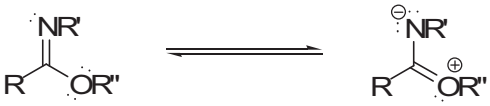


Figure 4.4.

The C=N double bond vibrations of amidines fall in the range from 1658 cm^{-1} to 1582 cm^{-1}. In contrast, the C=N double bond vibrations of imidates lies in the range from 1670 cm^{-1} to 1646 cm^{-1} which is close to the values obtained for unconjugated imines. Again these data suggest that the resonance for imidates is not so important.

Imidates are weaker bases than aliphatic amines, while unsubstituted amidines are stronger bases. In table 4.5 some characteristic pKa values are collected.[15]

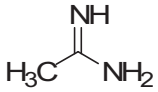
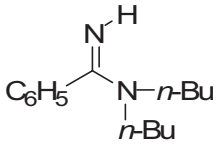
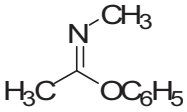
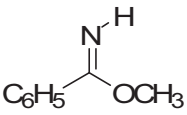
Compound	Formula	pKa	Solvent
ammonia	NH_3	9.245	water
methylamine	CH_3NH_2	10.624	water
aniline	$C_6H_5NH_2$	4.65	water
acetamidine		12.40	water
N,N-di-*n*-butylbenzamidine		11.27	50% aq methanol
phenyl N-acetimidate		6.2	water
methyl benzimidate		5.6	water

Table 4.5. *pK_a-values of some nitrogen bases.*

The conformation of imidates is presented in figure 4.5.[16] For ring imidates with an exocyclic oxygen function where n= 2→8, the conformation is *syn* because of steric requirements. However, when the ring size increases (n= 9→13), the imidates tend to exist in the *anti* form. Open-chain analogues exist also in the *anti* configuration. It is suggested that this is due to interorbital electron repulsion between the non-bonding electrons on oxygen and the lone pair localised in an sp^2 orbital on nitrogen. High barriers for interconversion of the *syn* and *anti* forms of O-imidates were observed.[16]

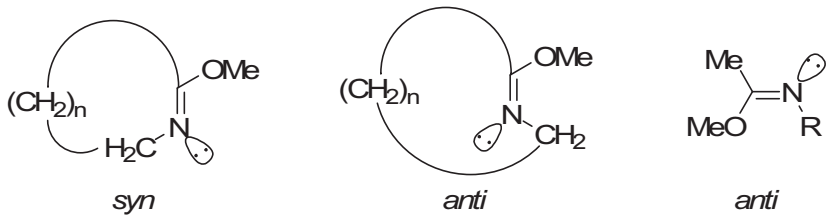


Figure 4.5. *Imidate conformation.*

Imidates are known to be very useful synthetic building blocks and pharmacophores, hence the interest in their preparation.[17] The classical method to synthesize imidates is the Pinner reaction.[18,19] Hereby, a nitrile is condensed with an alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide at 0℃ (Figure 4.6).

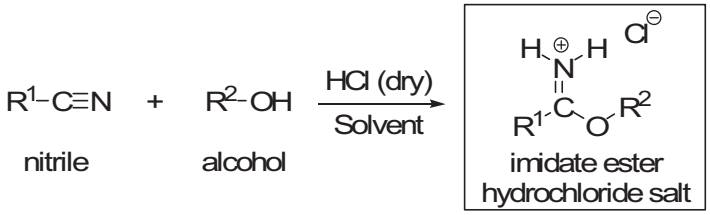


Figure 4.6. *Pinner Reaction.*

Since the pioneering work of Pinner, several new methods to synthesize imidate esters have been developed[14], e.g. a base-catalyzed reaction of nitriles with alcohols[20]; reaction of amines with orthoesters[21]; a modified Staudinger ligation[22]; a three-component coupling of terminal alkynes, sulfonyl azides and an alcohol in the presence of a copper catalyst[23]; a palladium-catalyzed insertion of isonitriles into *ortho* bromo arylalcohol[24]; three-component coupling using arynes, isonitriles and aldehydes.[25]

4.4 DEFINITION OF THE PROBLEM

Nitrogen-containing ligands are known as cheap, easily accessible and stable alternatives for phosphane ligands. As a result, the design, synthesis and application of a wide variety of nitrogen ligands has received a lot of attention, e.g. oxazolines (**4.10**)[26], semicorrins (**4.11**)[27], diimines (**4.12**)[28], salen (**4.13**)[29], 2,2'-bipyridines (**4.14**)[30], amidines (**4.15**)[31] and sulfoximines (**4.16**)[32] (Figure 4.7).

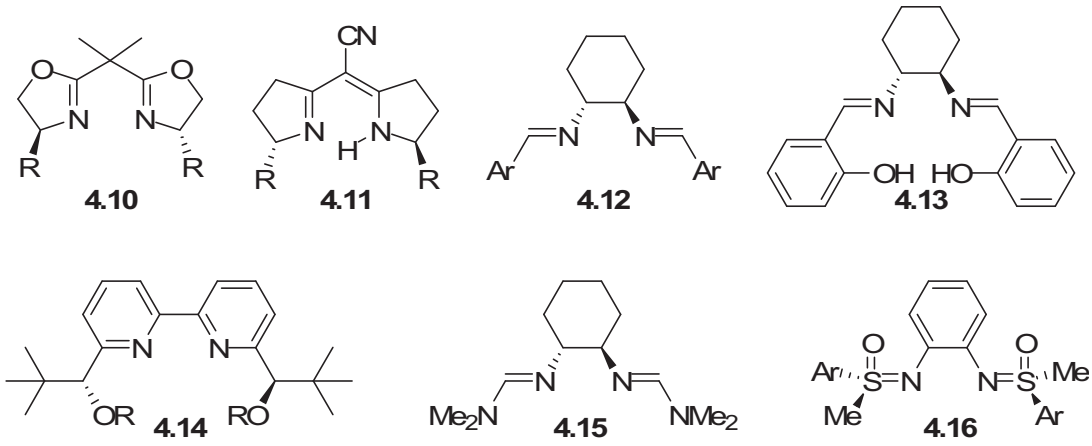
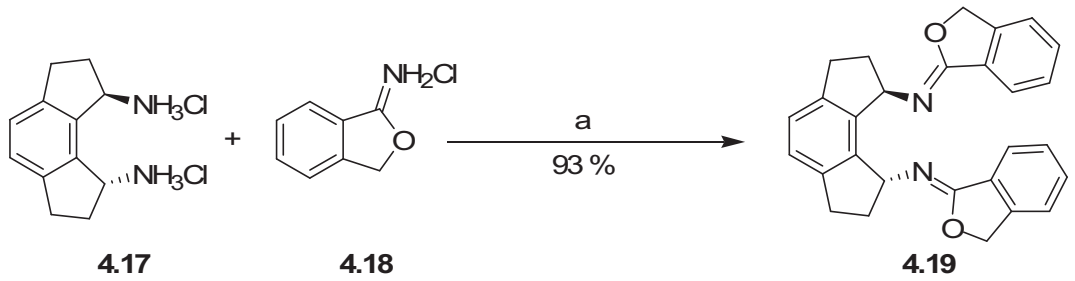


Figure 4.7. *Chiral nitrogen-containing ligands.*

Surprisingly, imidates have never been used as ligands in catalysis. Their usage was probably precluded due to their generally assumed instability.

In an attempt to find a stable alternative for diimine ligands, Vandyck synthesized bisimidate **4.19** via a condensation of cyclic imidate ester **4.18** with chiral *as*-indaceen bisamine **4.17**.[33] Ligand **4.19** was tested in Cu(I)-catalyzed asymmetric cyclopropanations, however, no reaction occurred.



4.17 **4.18** **4.19**

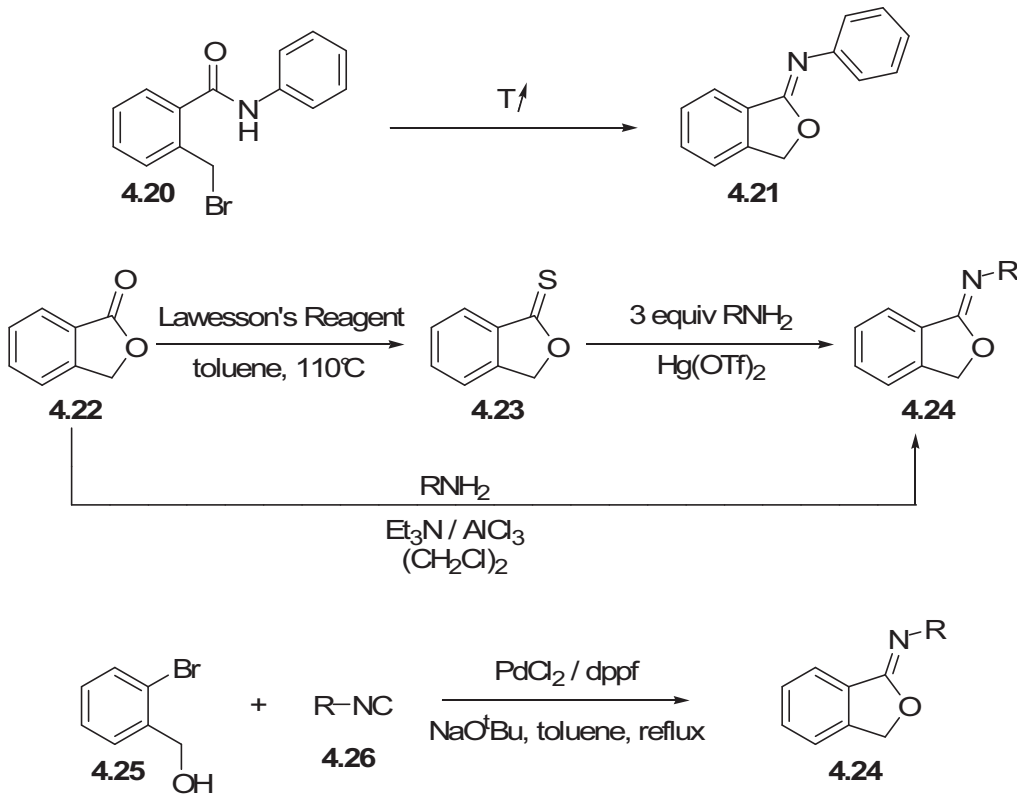
Scheme 4.1. *Synthesis of bisimidate ester (**4.19**): a) 2.9 eq **4.18**, 5.5 eq Et_3N, CH_2Cl_2, RT, 24u.*

Although the first results were disappointing, a further and more thorough investigation of this imidate ligand family was necessary. In this chapter, we will present the synthesis of several bisimidates with various backbones and their application in several asymmetric test reactions. In addition, we have developed a synthesis for substituted imidates. And to conclude, mixed phosphorous-imidate ligands are synthesized.

4.5 SYNTHESIS OF IMIDATE LIGANDS

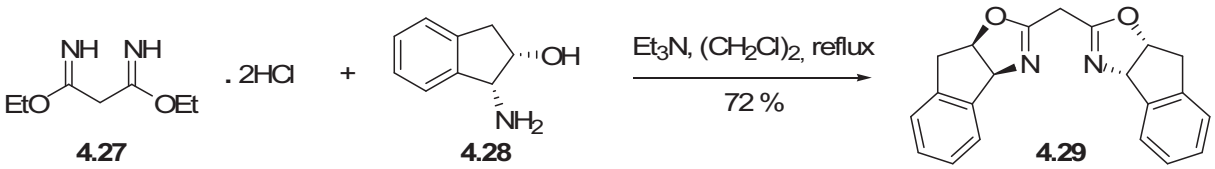
4.5.1 Synthesis of 1,3-dihydro-iminoisobenzofuran hydrochloride (4.18)

The synthesis of cyclic imidate esters is described in the literature. 2-Bromomethylbenzanilide **4.20** forms the corresponding imidate ester **4.21** upon heating, however low yields are usually obtained.[34] A second possibility is starting from 1-thionophthalide **4.23** in the presence of $Hg(OTf)_2$.[35] High yields are obtained but a major drawback is the necessity to use 3 equivalents of amine which is not interesting for the synthesis of bidentate imidate ligands. Phthalides **4.22** can be directly converted into imidate ester **4.24** in low yield.[36] A palladium-catalyzed insertion of isonitriles **4.26** into 2-bromobenzyl alcohol **4.25** affords cyclic imidates **4.24** in good yield.[24a] The drawbacks of this method is the disagreeable odour of isonitriles[37] and the fact that chiral isonitriles are not commercially available (Scheme 4.2).



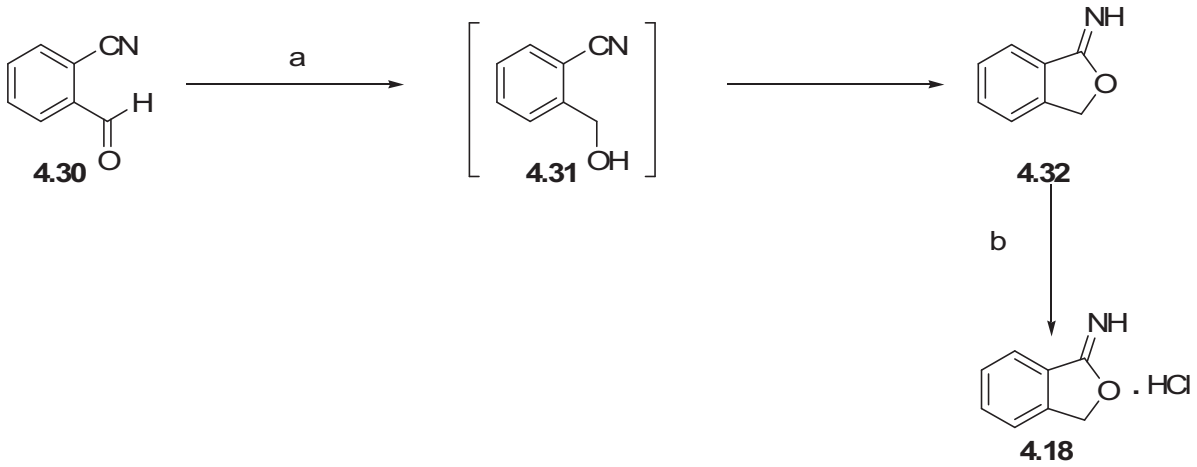
Scheme 4.2. *Literature results for the synthesis of cyclic imidates.*

A better approach would be the condensation of an imidate ligand precursor **4.18** with an appropriate amine, in analogy with the reaction of imidate esters **4.27** and amino alcohols **4.28** to oxazolines **4.29** (Scheme 4.3).[38]



Scheme 4.3. *Synthesis of oxazoline ligands by reaction of an aminoalcohol **4.28** with an imidate ester hydrochloride **4.27***

The synthesis of the imidate ligand precursor **4.18** is known in the literature via a Pinner reaction starting from *ortho*-cyanobenzylalcohol **4.31**.[39] Surprisingly, we found that the cyclic imidate ester was immediately formed after treatment of 2-cyanobenzaldehyde **4.30** with $NaBH_4$ in EtOH (Scheme 4.4). This was confirmed by IR spectroscopy where no characteristic IR absorption of a nitrile functionality could be detected. The free imidate base **4.32** was a -slightly impure- brownish oil. When the free imidate base was treated with HCl in dry Et_2O a very pure crystalline HCl salt **4.18** was formed. This one-step procedure was easily scaled up (8.3 g **4.18**, 92 % yield) and the product can be stored for years at -18°C without any sign of decomposition.



Scheme 4.4. *Synthesis of imidate hydrochloride* ***4.18****: a) $NaBH_4$, EtOH, -78℃→0℃, 35 min. b) HCl in dry Et_2O. 92% yield over both steps.*

4.5.2 Synthesis of a small imidate ligand library by condensation of imidate ligand precursor 4.18 with various chiral amines

In order to investigate the properties of this new ligand family, we decided to synthesize a small ligand library. In figure 4.8, various chiral amines are presented. These chiral amines were commercially available or synthesized in our laboratory.

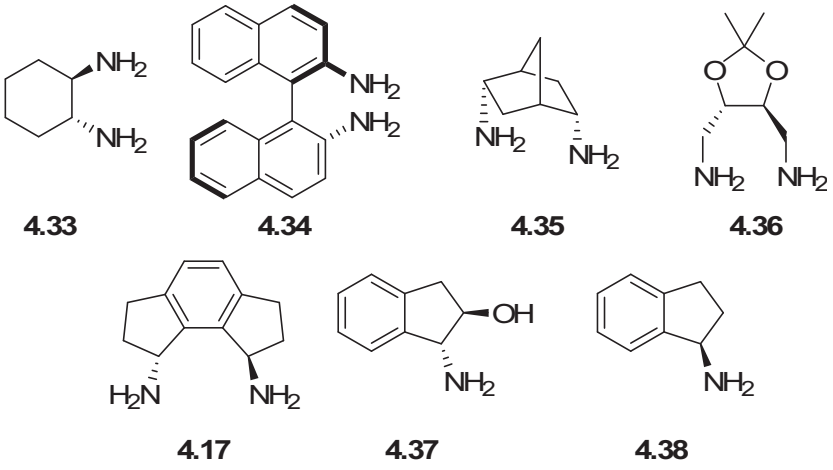
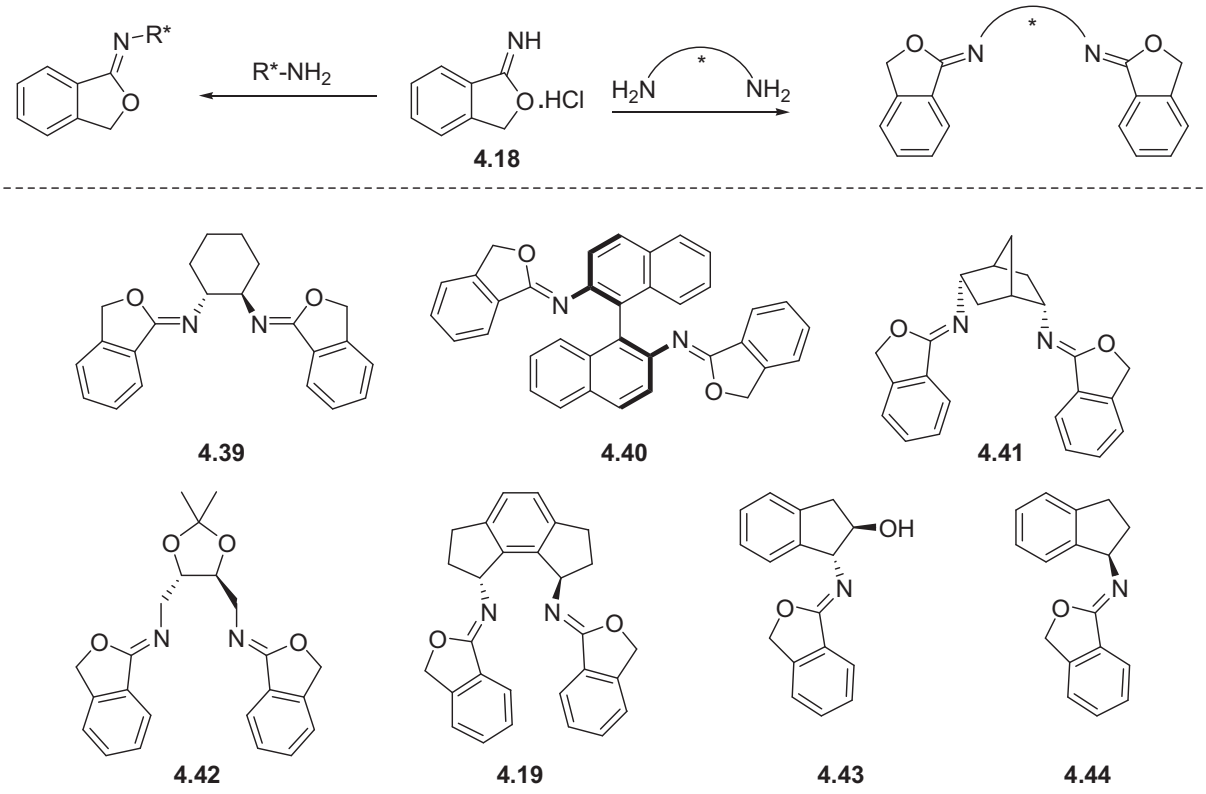


Figure 4.8. *Chiral amines.*

The C_2-symmetrical amines **4.33**[40], **4.34**[41], **4.35**[42], **4.36**[43] were chosen because their backbones are known to create very effective asymmetric environments.[44] Bisamine **4.17** was synthesized in our laboratory.[45] Monoamines **4.37** and **4.38** were selected to synthesize, respectively, a mixed imidate-hydroxyl ligand and a monodentate imidate ligand.

Condensation of these amines with the imidate precursor **4.18** in the presence of Et_3N resulted in the corresponding imidate ligands in excellent yields (Table 4.6).



entry	Amine	Product	Yield (%)
1	(1*R*,2*R*)-(-)-diaminocyclohexane (**4.33**)	**4.39**	85
2[b]	(*R*)-(+)-1,1'-binaphtyl-2,2'-diamine (**4.34**)	**4.40**	71
3	(1*S*,4*S*)-DIANANE (**4.35**)	**4.41**	56
4	(4*S*,5*S*)-4,5-di(aminomethyl)-2,2-dimethyldioxolane (**4.36**)	**4.42**	92
5	(1*R*,8*R*)-1,2,3,6,7,8-hexahydro-*as*-indacene-1,8-diamine (**4.17**)	**4.19**	93
6[c]	(1*R*,2*R*)-(-)-trans-1-amino-2-indanol (**4.37**)	**4.43**	91
7[c]	*R*-(-)-aminoindane (**4.38**)	**4.44**	74

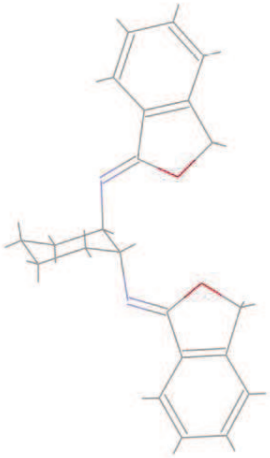
[a] ***Reagents and conditions***: amine (1 equiv), **4.18** (2.6 equiv), Et_3N (13 equiv), CH_2Cl_2.
[b] Reflux in MeOH.
[c] 1.3 equiv of **4.18**.

Table 4.6. *Synthesis of imidate ligands.*

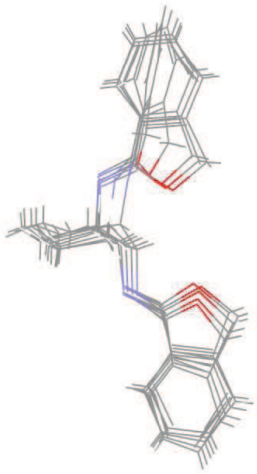
All reactions were performed in dry CH_2Cl_2 at room temperature. When the reaction was performed at reflux temperature, the reaction was finished faster. The condensation reaction with **4.34** as chiral amine was an exception. With CH_2Cl_2 as a solvent at refluxtemperature, no conversion was observed even after 24h. Therefore, we chose $ClCH_2CH_2Cl$ as a solvent with a higher boiling point. A marginal amount of product **4.40** was formed after one night, however, prolonged reaction times resulted in decomposition of the target molecule. Use of other bases, such as DBU and DIPEA, gave no improvement. Also the use of DMF as a solvent or microwaves did not result in the desired product. A breakthrough was achieved when the reaction was performed in protic solvents. The best result was obtained with MeOH as a solvent. After 5 days, the bidentate ligand **4.40** was almost exclusively formed (72% yield). No trace of decomposition products was noticed.

4.5.3 Synthesis of a copper complex of bisimidate 4.39

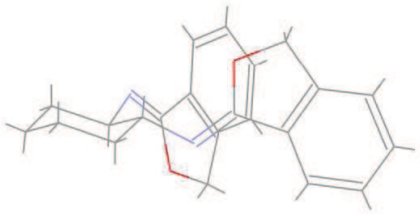
A study by molecular modelling towards the structure of bisimidate **4.39** revealed that the imidate groups were axially orientated (Figure 4.9). This was confirmed by ^{1}H NMR, bisimidate **4.39** showed for the alfa-protons on the cyclohexane ring two small vicinal coupling constants (dd, *J*= 3.9, 4.7 Hz) suggesting an axial position of the imidate groups. The flipped chair, where the imidate groups are equatorally orientated, differs 8.002 kJ/mol from the global minimum.



Global minimum of **4.39** (ax-ax **4.39**)



All conformers that differ up to 5 kJ/mol from the global minimum.



Flipped Chair (eq-eq **4.39**): differs 8.002 kJ/mol from the global minimum.

Figure 4.9. *Molecular modelling of bisimidate* ***4.39****.*

The potential for bisimidate **4.39** to act as a ligand was investigated by treating **4.39** with $Cu(CH_3CN)_4PF_6$ in CH_3CN. Suitable crystals for X-ray diffraction were grown from a solution of the complex in MTBE/CH_3CN. An X-ray structure was obtained, shown in figure 4.10**.** This revealed that in the complex the opposite chair conformation was adopted, with the imidate groups in equatorial position and therefore suitable for complexation with Cu(I). The Cu(I)-complex shows a tetrahedral arrangement with two bidentate ligands around the metal. The Cu-N bond lengths are 2.07 Å and 2.05 Å for both ligands. The angles between N(2)-Cu(1)-N(9) and N(28)-Cu(1)-N(35) are respectively 84.0° and 84.4°. The imidate groups clearly possess the (*Z*)-geometry dissecting the space around the metal effectively in a C_2-fashion.

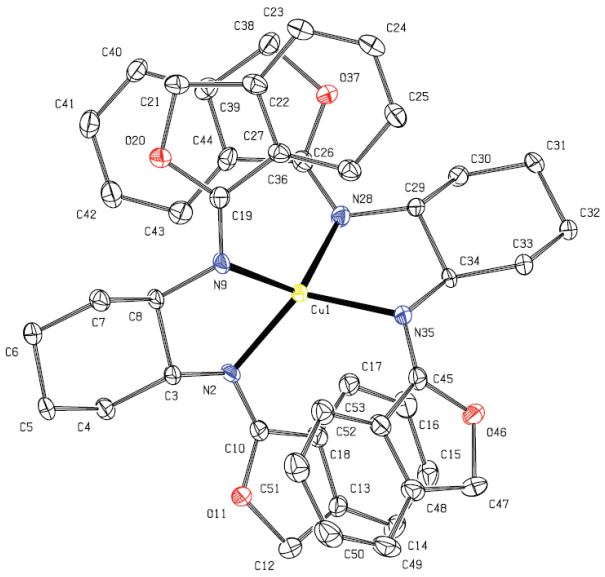
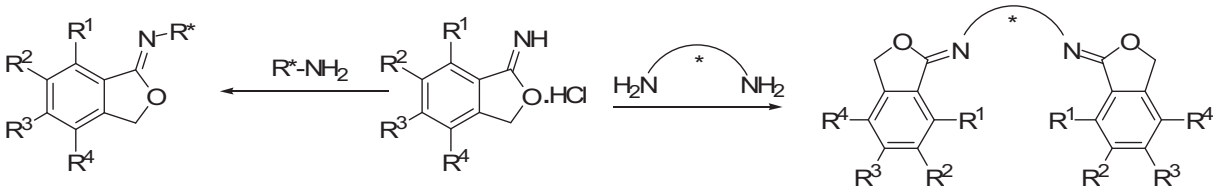


Figure 4.10. *X-ray structure of Cu(**4.39**)$_2$.PF$_6$. Hydrogens and PF$_6$ are omitted for clarity. Selected distances, bond angles and torsion angles: Cu(1)-N(2) 2.065 Å, Cu(1)-N(9) 2.054 Å, Cu(1)-N(28) 2.078 Å, Cu(1)-N(35) 2.046 Å; N(2)-Cu(1)-N(9) 84.02°, N(2)-Cu(1)-N(28) 127.49°, N(2)-Cu(1)-N(35) 120.08°, N(9)-Cu(1)-N(28) 117.70°, N(9)-Cu(1)-N(35) 128.75°, N(28)-Cu(1)-N(35) 84.41°, N(2)-C(3)-C(8)-N(9) -49.6°, N(28)-C(29)-C(34)-N(35) -46.7°.*

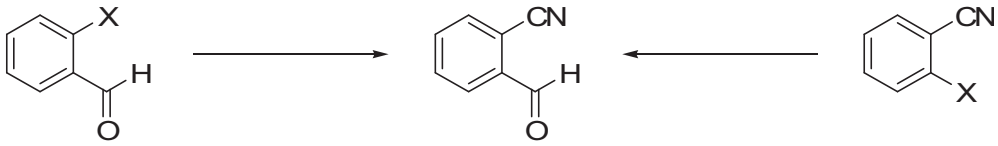
4.5.4 Synthesis of substituted imidate precursors

In an attempt to broaden the scope of the imidate ligand family, we wanted to put substituents on the aromatic ring of the imidate ligand precursor (Scheme 4.5). These substituents are important to modulate the electron density of the imidate. Complex Cu(**4.39**)$_2$.PF$_6$ contained two imidate ligands for each copper atom. Substituents on the R^1 position of the imidate would increase the steric bulk around the metal and, hence, it would be possible to synthesize copper species with only one ligand on the metal.



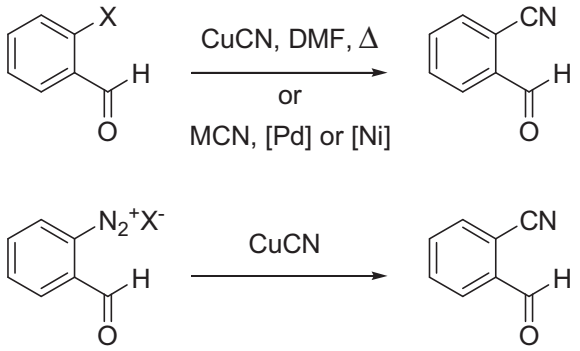
Scheme 4.5. *Synthesis of substituted imidate ligands*

Unfortunately, there were no substituted *ortho*-formylbenzonitriles commercially available. Therefore, we needed to find a simple and easily upscalable synthetic route towards these compounds. There are two fundamentally different approaches: an introduction of a cyano group or an introduction of a formyl group on the aromatic ring (Scheme 4.6).



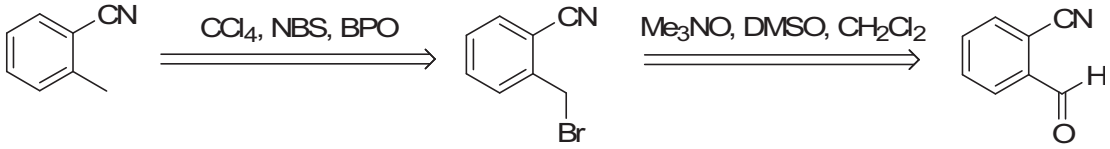
Scheme 4.6. *Two different approaches to the design of ortho-formylbenzonitriles.*

A classical procedure to introduce a nitrile on an aromatic ring is via a Rosenmund-von Braun reaction.[46] Hereby, aryl halides are cyanated with an excess of copper(I)cyanide in a polar high-boiling solvent such as DMF at reflux temperature. Drawbacks of this type of reaction is the requirement of stoichiometric amounts of CuCN, the necessity to protect the aldehyde under the severe reaction conditions and the low reactivity of aryl chlorides and bromides (in general the use of expensive aryl iodides is required).[47]
More recently, palladium-[48] and nickel-catalyzed[49] aryl cyanation methods have been developed as milder alternatives to the classic Rosenmund-von Braun reaction. Although many successful applications of the palladium-catalyzed aryl cyanation reaction have been documented, the method suffers from poor reliability.[50]
Also interesting is the Sandmeyer reaction where aryl nitriles are synthesized from aryldiazonium salts.[51]



Scheme 4.7. *Introduction of cyano group on the aromatic ring.*

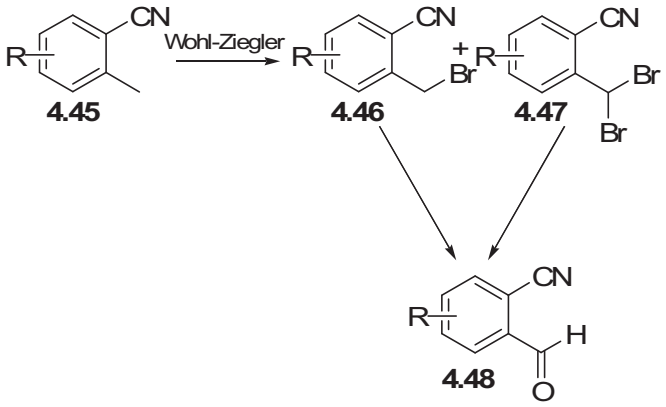
Introduction of a formyl group on the aromatic ring can easily happen via a two-step procedure starting from commercially available substituted 2-methylbenzonitriles (Scheme 4.8).[52] Given the mild conditions of this procedure, we preferred this method for the synthesis of the *ortho*-formylbenzonitriles.

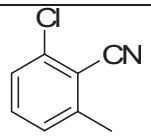
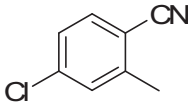
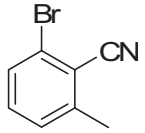
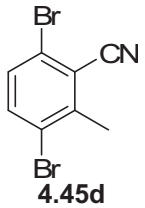


Scheme 4.8. *Introduction of a formyl group on the aromatic ring.*

A Wohl-Ziegler reaction with 1.1 equiv NBS resulted in certain cases in a mixture of monobrominated **4.46** and dibrominated product **4.47**. This resulted in lower yields and a difficult separation of both compounds. Oxidation of **4.46** with Me_3NO resulted in the corresponding formylbenzonitrile **4.48** in low yield (48-67%). When a mixture of **4.46** and **4.47** was used in the oxidation reaction, only the monobrominated product

formed the corresponding formylbenzonitrile **4.48** while the dibrominated product remained unchanged. Because of the loss of a significant amount of product, we tried to find another procedure.[53] When a Wohl-Ziegler reaction was performed with 3 equiv NBS, we obtained selectively the dibrominated product **4.47a-b** in excellent yields (94-96%). Hydrolysis of **4.47a-b** with $AgNO_3$ in CH_3CN/H_2O delivered the target product (**4.48a-b**) in high yields (83-90%).
On the other hand, for **4.45c**, a mixture of **4.46c** and **4.47c** was obtained with method B even after prolonged reaction times. For **4.45d**, only the formation of monobrominated product was observed. However, it was impossible to form the corresponding aldehyde **4.48d**. This was probably due to the high sterical hindrance.

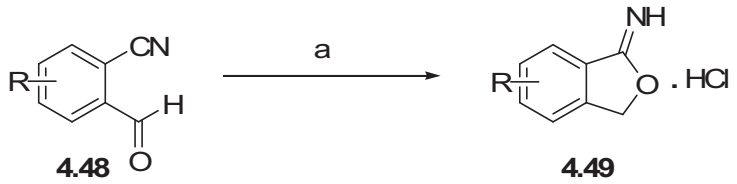


	Method A[a]			Method B[b]		
	Mono-brominated	Di-brominated	Aldehyde	Mono-brominated	Di-brominated	Aldehyde
 **4.45a**	82% (**4.46a**)	n.d.[c]	67% (**4.48a**)	n.d.[c]	94% (**4.47a**)	90% (**4.48a**)
 **4.45b**	57% (**4.46b**)	24% (**4.47b**)	48-53% (**4.48b**)	n.d.[c]	96% (**4.47b**)	83% (**4.48b**)
 **4.45c**	-	-	-	44% (**4.46c**)	46% (**4.47c**)	76% (**4.48c**)
 **4.45d**	-	-	-	35% (**4.46d**)	n.d.	n.r.[d,e]

[a] ***Reagents and conditions:*** Method A: (i) methylbenzonitrile (1 equiv), NBS (1.1 equiv), benzoylperoxide (3 mol%), CCl_4. (ii) bromomethylbenzonitrile (1 equiv), Me_3NO (4 equiv), DMSO, CH_2Cl_2.
[b] ***Reagents and conditions:*** Method B: (i) methylbenzonitrile (1 equiv), NBS (3.0 equiv), benzoylperoxide (3 mol%), CCl_4. (ii) dibromomethylbenzonitrile (1 equiv), $AgNO_3$ (4.0 equiv), CH_3CN, H_2O.
[c] n.d.: not detected.
[d] n.r.: no reaction occurred.
[e] ***Reagents and conditions:*** bromomethylbenzonitrile (1 equiv), Me_3NO (4 equiv), DMSO, CH_2Cl_2.

Table 4.7. *Synthesis of ortho-formylbenzonitriles.*

As with the unsubstituted *ortho*-formylbenzonitrile, formation of the substituted cyclic imidate ester (**4.49**) occurred smoothly with $NaBH_4$ in EtOH (Table 4.8).



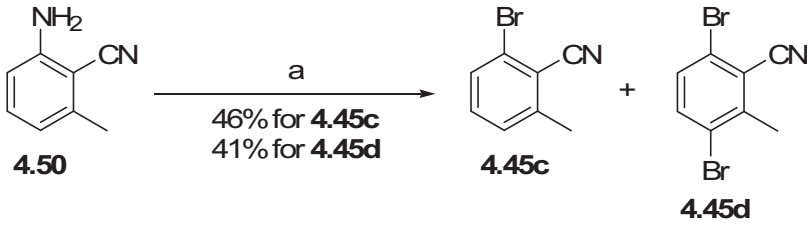
4.48 **4.49**

Entry	*ortho*-formylbenzonitrile	Cyclic imidate ester
1	**4.48a**	94% (**4.49a**)
2	**4.48b**	96% (**4.49b**)
3	**4.48c**	69% (**4.49c**)

[a] ***Reagents and conditions:*** (i) $NaBH_4$, EtOH, -78℃ →0℃, 35 min. (ii) HCl in dry Et_2O.

Table 4.8. *Synthesis of substituted cyclic imidate esters.*

2-Bromo-6-methylbenzonitrile (**4.45c**) is not commercially available, however, it could be easily synthesized starting from the corresponding 2-amino-6-methylbenzonitrile via a Sandmeyer reaction. Arylbromides can also be prepared from primary aromatic amines in one step by treatment of the amine with *tert*-butyl nitrite and anhydrous $CuBr_2$ in anhydrous acetonitrile at 65℃. [54] This procedure is in fact a combination of a diazotization and a Sandmeyer reaction. An additional advantage is that cooling to 0℃ is not needed. It was reported that a substitution of a bromide at the aromatic ring positions *ortho* and *para* to the original amine position can take place.[54] With arylamines that do not possess *para* substituents, orientation of the bromine to the *para* position is highly favored.
This is what we also observed when the reaction was performed on **4.50**: **4.45c** and **4.45d** were formed in almost equimolar amounts (Scheme 4.9).



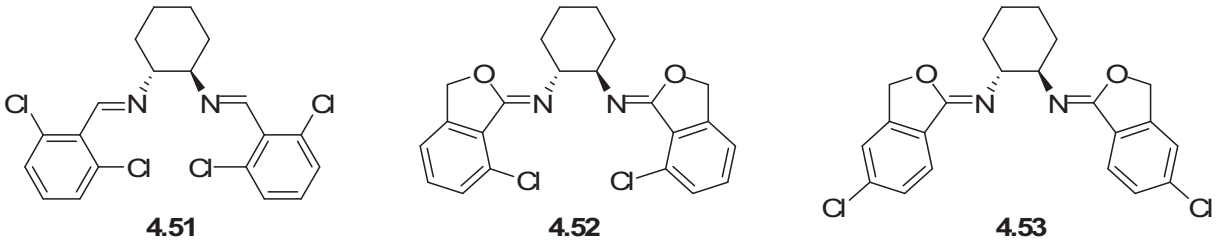
4.50 **4.45c** **4.45d**

$$2\ ArNH_2 + 2\ t\text{-BuONO} + CuBr_2 \rightarrow 2\ ArBr + CuO + H_2O + 2\ N_2 + 2\ t\text{-BuOH}$$

Scheme 4.9. *Synthesis of **4.45c** and **4.45d**: a) arylamine (1 equiv), $CuBr_2$ (1.2 equiv), tert-butyl nitrite (1.5 equiv), CH_3CN.*

4.5.5 Synthesis of chlorine-substituted bisimidate ligands and their corresponding copper(I) complexes

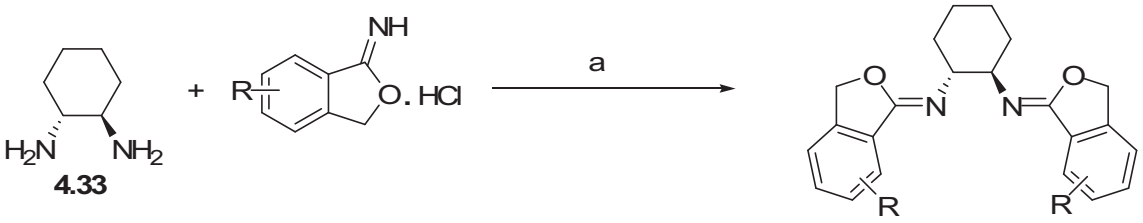
In analogy with Jacobsen's imine **4.51** where *ortho* chlorine substituents on the phenyl ring resulted in a highly effective ligand in aziridination reactions (cf. Chapter 4.7.1), we synthesized bisimidate ligands **4.52** and **4.53** (Figure 4.11).



4.51 **4.52** **4.53**

Figure 4.11. *Chlorine-substituted bisimine and bisimidate ligands.*

The synthesis was carried out according to our typical procedure (Table 4.9). The lower yield with imidate ester **4.49a** was attributed to the increasing bulk *ortho* to the imidate nitrogen. (Table 4.9, entry 1)



4.33

Entry	Imidate ester	Yield bisimidate
1	**4.49a**	50% (**4.52**)
2	**4.49b**	75% (**4.53**)

[a] ***Reagents and conditions:*** **4.33** (1 equiv), imidate ester (2.6 equiv), Et_3N (13 equiv), CH_2Cl_2.

Table 4.9. *Synthesis of chlorine-substituted imidate ligands.*

Next, the corresponding copper(I) complexes were synthesized from bisimidates **4.52** and **4.53** by treating them with $Cu(CH_3CN)_4PF_6$ in CH_3CN. Unfortunately, several attempts to obtain suitable crystals for X-ray diffraction have all failed. The Cu(I)-complex of **4.52** resulted in a white powder while the corresponding complex of **4.53** resulted in a yellow powder like Cu(**4.39**)$_2$.PF_6. Next, ES-MS of the different complexes were recorded. The largest mass peak for the copper(I) complexes of **4.39** and **4.53** was attributed to respectively $[Cu(\mathbf{4.39})_2]^+$ and $[Cu(\mathbf{4.53})_2]^+$. In sharp contrast, the largest mass peak for the copper(I) complex of **4.52** was attributed to $[Cu(\mathbf{4.52})]^+$ (Figure 4.12). These results, together with the different colour, indicates that an increasing sterical bulk around the metal indeed results in the formation of a copper species with only one ligand around the metal.

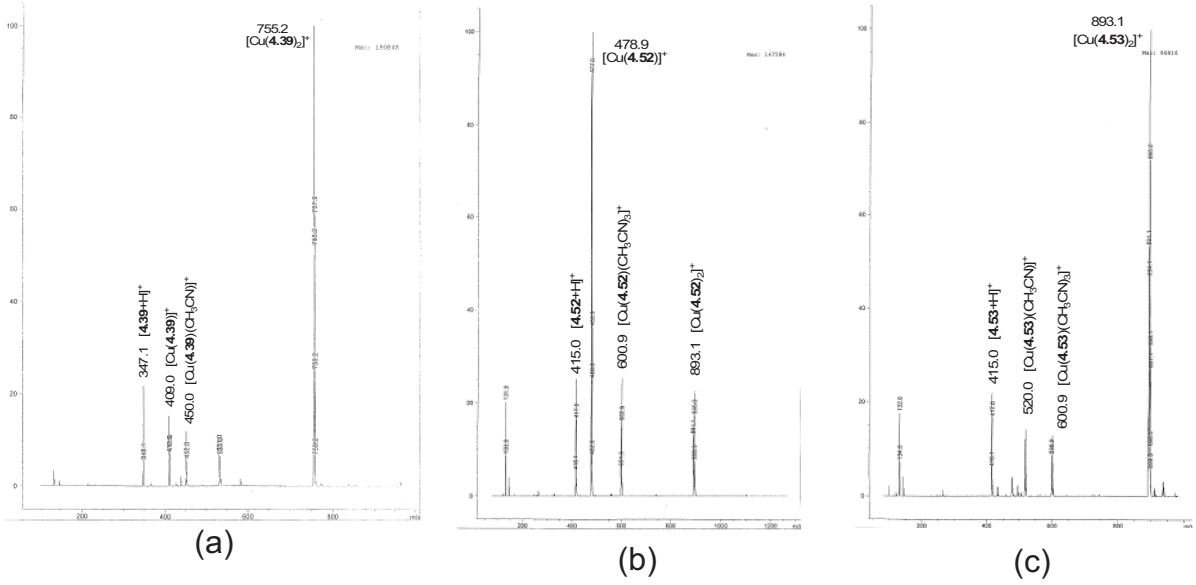


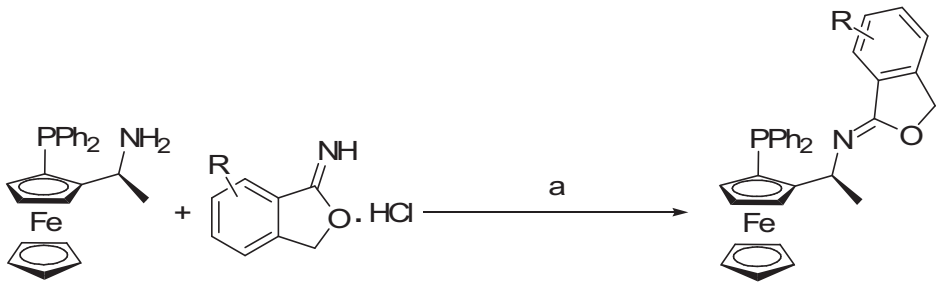
Figure 4.12. *Electro Spray Mass Spectra of copper(I) complexes of (a) ligand* ***4.39****, (b) ligand* ***4.52*** *and (c) ligand* ***4.53****.*

4.5.6 Synthesis of mixed imidate-phosphane ligands

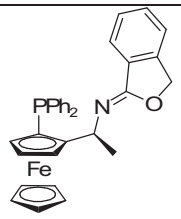
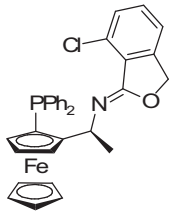
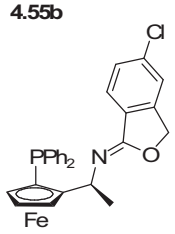
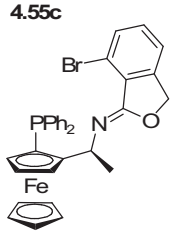
A literature survey of the different ligand structures reveals that a large number of them are C_2-symmetrical.[55] The presence of C_2-symmetry in a ligand can be advantageous because it reduces the number of possible catalyst-substrate arrangements and, consequently, the number of reaction pathways and transition states. This feature can have a beneficial effect on the enantioselectivity because competing less-selective pathways are possibly eliminated. In addition, C_2-symmetry is of particular advantage in mechanistic and structural studies because it facilitates the analysis of the ligand-substrate interactions that may be responsible for enantioselection. However, there is no fundamental reason why a non- C_2-symmetrical ligand should be inferior to a C_2-symmetrical ligand. For certain reactions, nonsymmetrical ligands could allow more effective enantiocontrol than C_2-symmetrical ligands, e.g. transition metal-catalyzed asymmetric allylic alkylations.

From this point of view, we wanted to synthesize mixed phosphane-imidate ligands because of the distinctly different characteristics of the P-atom and the N-atom. Very recently, several aminophosphane ligands became commercially available from Sigma-Aldrich.[56] We chose ferrocenylaminophosphanes **4.54** as the most interesting compound because they are known to be air-stable[57] and they represent a convenient source of chirality for ligand construction.[58]

Synthesis of the mixed imidate-phosphane ligands (**4.55a-d**) occurred smoothly in one step via our typical condensation procedure (Table 4.10). For non sterically hindered imidate esters, high yields were obtained (Table 4.10, entries 1 and 3). However, when the reaction was performed with more sterically demanding imidate esters lower conversions were obtained (Table 4.10, entries 2 and 4).



4.54 **4.55a-d**

Entry	Imidate Ester	Imidate-phosphane	Yield (%)
1	**4.18**	 **4.55a**	97
2	**4.49a**	 **4.55b**	61
3	**4.49b**	 **4.55c**	99
4	**4.49c**	 **4.55d**	51

[a] ***Reagent and conditions***: (R_p)-1-[(1*S*)-(1-aminoethyl)]-2-(diphenylphosphino)-ferrocene (1 equiv), imidate ester (1.3 equiv), Et_3N (3 equiv), CH_2Cl_2, reflux.

Table 4.10. *Synthesis of mixed imidate-phosphane ligands.*

4.6 SYNTHETIC APPLICATIONS OF IMIDATES

4.6.1 One-step synthesis of chiral oxazoline-alcohol ligands

Chiral oxazolines bearing a hydroxyl substituent show excellent catalytic activity in the asymmetric addition of diethylzinc to aldehydes.[59] Bolm *et al.* studied the role of planar chirality versus central chirality in ferrocene ligands (Figure 4.13).[60,61] The combination of the proper planar chirality and central chirality resulted in a highly active ligand **4.56**. Remarkably, ligand **4.57** containing only the central chirality gave also high enantioselectivity and catalytic activity.[61]

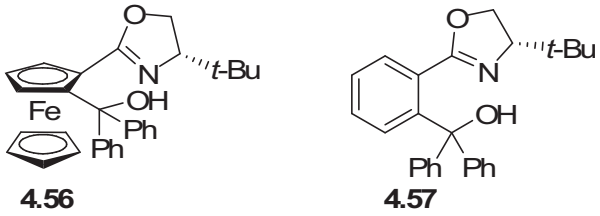
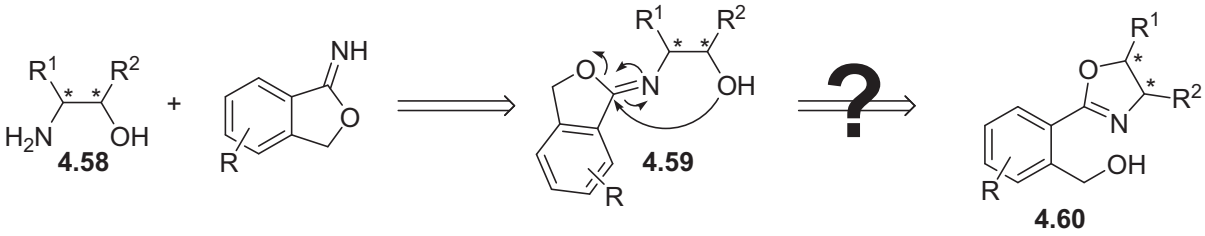


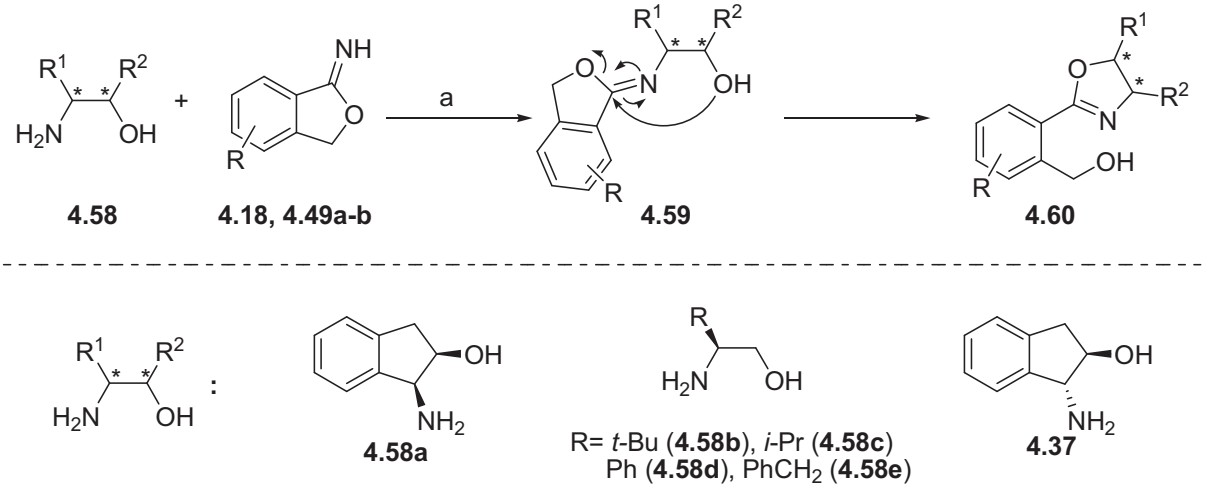
Figure 4.13. *Oxazoline ligands developed by Bolm and coworkers.*

It is known that the synthesis of oxazolines can happen efficiently via reaction of an aminoalcohol and an imidate ester. As a result, substituents at the two position of the oxazoline moiety can be incorporated.[62] From this point of view, we wondered if it would be possible to use cyclic imidate esters in the synthesis of oxazolines (Scheme 4.10). Because of the use of a cyclic imidate ester, the required hydroxyl-functionality would immediately be incorporated in the ligand structure.



Scheme 4.10. *Synthetic scheme towards oxazoline-alcohol ligands.*

Condensation of imidate esters (**4.18**, **4.49a-b**) with several aminoalcohols resulted in the corresponding oxazoline ligands or imidate ligands (Table 4.11) (Figure 4.14). No formation of the imidate alcohols was observed for (1*S*,2*R*)-*cis*-1-amino-2-indanol, (*S*)-*tert*-leucinol and (*S*)-valinol; the oxazoline alcohol was obtained in quantitative yield (Table 4.11, entries 1,3 and 4). However, with (*S*)-phenylglycinol and (*S*)-phenylalaninol a mixture of imidate alcohol and oxazoline alcohol was formed (Table 4.11, entries 5-6). Separation of the two components via preparative HPLC was impossible, suggesting that the energy difference between oxazoline and imidate is too small to form one exclusively. With (1*R*,2*R*)-*trans*-1-amino-2-indanol, it was possible to selectively form the imidate alcohol (Table 4.11, entry 2). The condensation of the substituted imidate esters (**4.49a-b**) with (1*S*,2*R*)-*cis*-1-amino-2-indanol resulted again in the corresponding oxazolineligands (**4.60d-e**) in good yield (Table 4.11, entries 7-8).



Entry	Imidate ester	aminoalcohol	Yield imidate (%)[b]	Yield oxazoline (%)[b]
1	**4.18**	(1*S*,2*R*)-*cis*-1-amino-2-indanol (**4.58a**)	n.d.	Quant. (**4.60a**)
2	**4.18**	(1*R*,2*R*)-*trans*-1-amino-2-indanol (**4.37**)	91 (**4.43**)	n.d.
3	**4.18**	(*S*)-*tert*-leucinol (**4.58b**)	n.d.	Quant. (**4.60b**)
4	**4.18**	(*S*)-valinol (**4.58c**)	n.d.	Quant. (**4.60c**)
5[c]	**4.18**	(*S*)-2-phenylglycinol (**4.58d**)	48.3	51.7
6[c]	**4.18**	(*S*)-phenylalaninol (**4.58e**)	30.9	69.1
7	**4.49a**	(1*S*,2*R*)-*cis*-1-amino-2-indanol (**4.58a**)	n.d.	83 (**4.60d**)
8	**4.49b**	(1*S*,2*R*)-*cis*-1-amino-2-indanol (**4.58a**)	n.d.	66(**4.60e**)

[a] ***Reagents and conditions***: aminoalcohol **4.58** (1 equiv), imidate ester (1.1 equiv), Et_3N (3 equiv), CH_2Cl_2, room temperature, 24h.
[b] n.d.: not detected.
[c] Unseparable mixture of imidate and oxazoline is formed.

Table 4.11. *Synthesis of imidate-alcohol ligands (**4.59**) and oxazoline-alcohol ligands (**4.60**).*

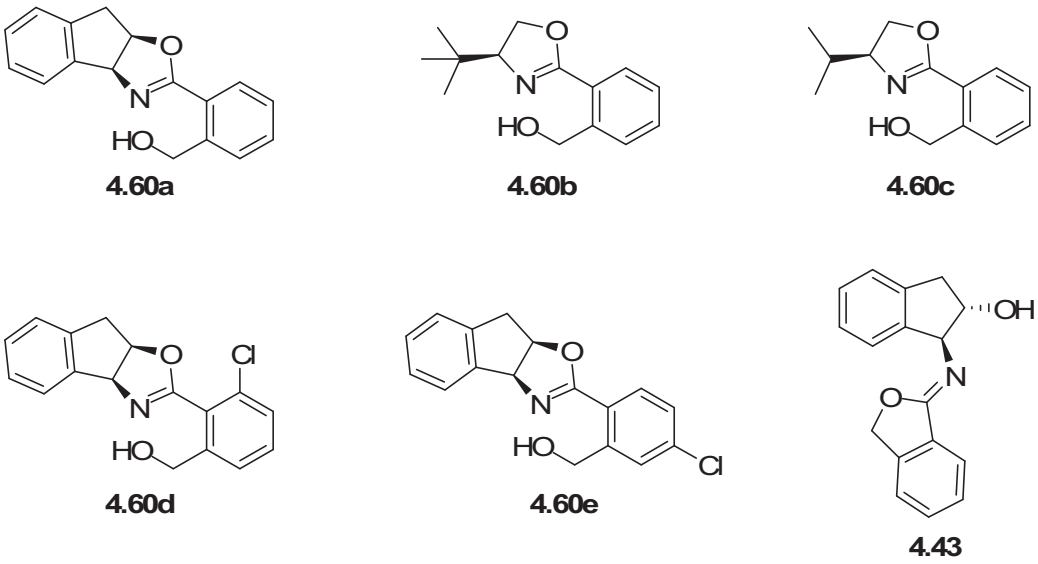


Figure 4.14. *Synthesized oxazoline- and imidate-alcohol ligands.*

Suitable crystals for X-ray diffraction were grown from a solution of **4.60a** in isooctane/Et_2O. An X-ray structure was obtained, shown in figure 4.15. The hydroxyl proton forms a hydrogen bond with the nitrogen of the oxazoline moiety. As a result, a stable seven-membered ring chelate is formed.

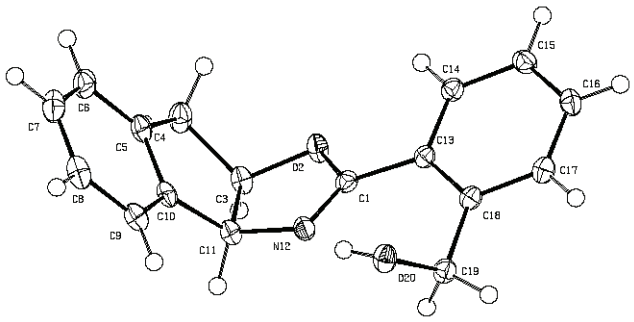
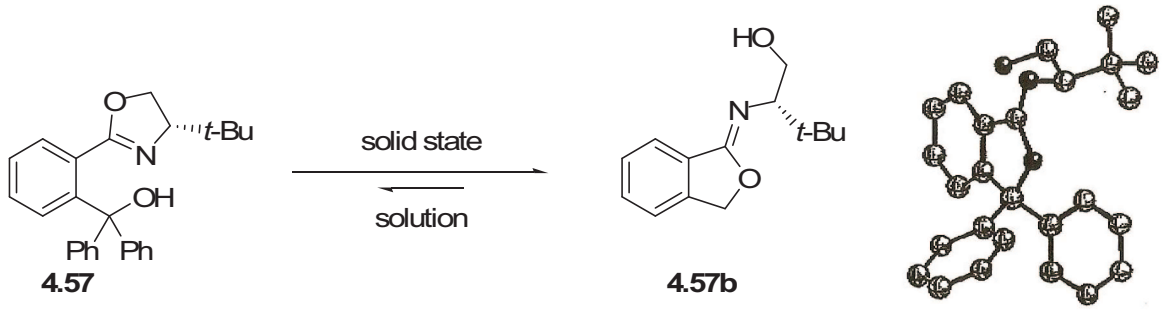


Figure 4.15. *X-ray structure of* ***4.60a****.*

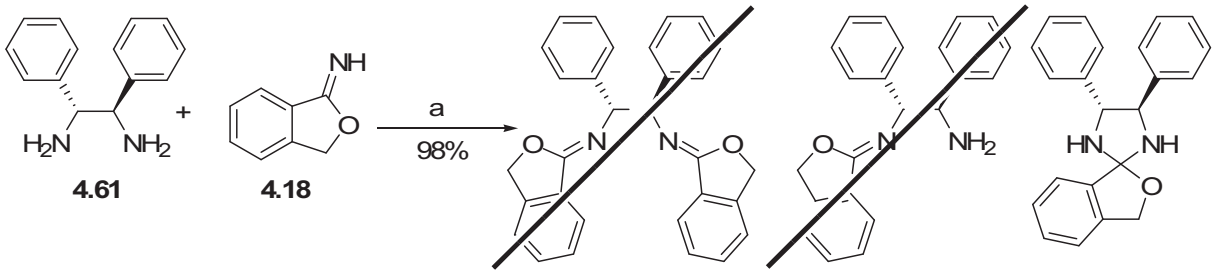
Interestingly, Bolm *et al.* found that a rearrangement from the oxazoline alcohol **4.57** to the imidate alcohol **4.57b** can occur in the solid state (Scheme 4.11).[63] It was assumed that this is due to the increasing rigidity of the imidate alcohol **4.57b** which results in a better packing of the molecules in the solid state. However, when the product was dissolved, the equilibrium was again shifted to the oxazoline alcohol product (**4.57**).



Scheme 4.11. *Rearrangement of oxazoline alcohol* ***4.57*** *to imidate alcohol* ***4.57b****.*

4.6.2 Synthesis of chiral imidazolidines

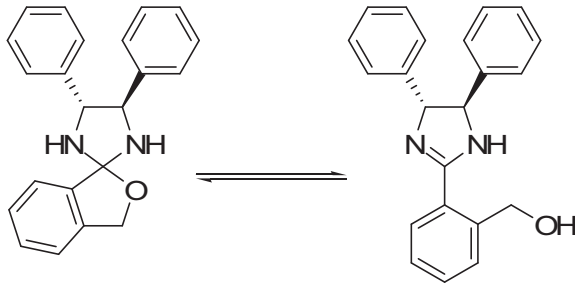
In an attempt to synthesize a small ligand library, we also selected (1*R*,2*R*)-(+)-diphenylethylenediamine (**4.61**) (cf. Chapter 4.5.2). However, when we tried to make the bidentate imidate ligand **4.62**, imidazolidine **4.64** was formed instead. We observed no characteristic infrared absorption originating from the imidates, however, a signal arising from the NH-bond was clearly visible (Scheme 4.12).



	4.62	4.63	4.64
Expected IR signals :	1689 cm^{-1}	1689 cm^{-1}	3265 cm^{-1}
Expected Mass $[M+H]^+$:	445.1	329.1	329.1
Observed IR signals :	no imidate vibration	no imidate vibration	3253.5 cm^{-1}
Observed Mass $[M+H]^+$:			329.1

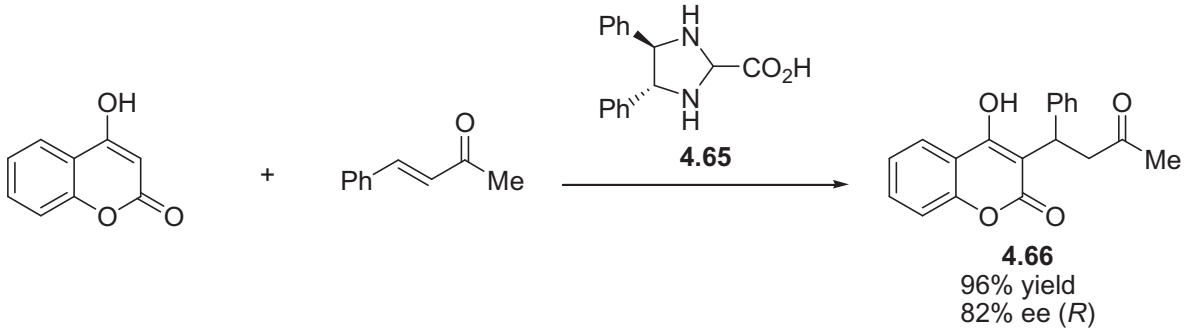
Scheme 4.12. *Synthesis of chiral imidazolidines: a) amine* ***4.61*** *(1 equiv),* ***4.18*** *(2.6 equiv),* Et_3N *(13 equiv),* CH_2Cl_2*, RT, 24h.*

Imidazolidines can be made by reacting **4.61** with one equivalent of an aldehyde or ketone. However, when a second equivalent is added a bidentate bisimine is formed.[64] In contrast, imidazolidine **4.64** is a very stable compound and no formation of a bidentate bisimidate ligand was observed with 2.6 equiv of **4.18** or after heating for several days. This is due to a reversible opening and closing of the furan moiety, the equilibrium being in favour of the spiro compound **4.64** (scheme 4.13).



Scheme 4.13. *Ring opening of the furan moiety of imidazolidine* ***4.64****.*

Chiral imidazolidines are typically used as organocatalysts in asymmetric Michael reactions[65] and asymmetric α-halogenations[66,67]. Jørgensen *et al.* used chiral imidazolidine **4.65** in the asymmetric synthesis of warfarin **4.66** (Scheme 4.14).[68] It could be interesting to test the potential of imidazolidine **4.64** as an organocatalyst in this type of test reactions.

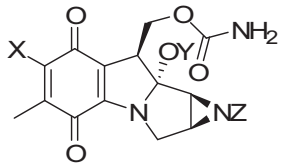


Scheme 4.14. *Organocatalytic asymmetric formation of warfarin (****4.66****) using a chiral imidazolidine catalyst (****4.65****).*

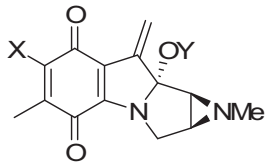
4.7 APPLICATION OF THE SYNTHESIZED CHIRAL LIGANDS

4.7.1 Copper(I)-catalyzed asymmetric aziridination[69,70]

A number of molecules in nature possess an aziridine ring. These compounds exhibit a potent biological activity, which is associated with the reactivity of the strained heterocycle. The best-known class are the Mitosanes (Figure 4.16).



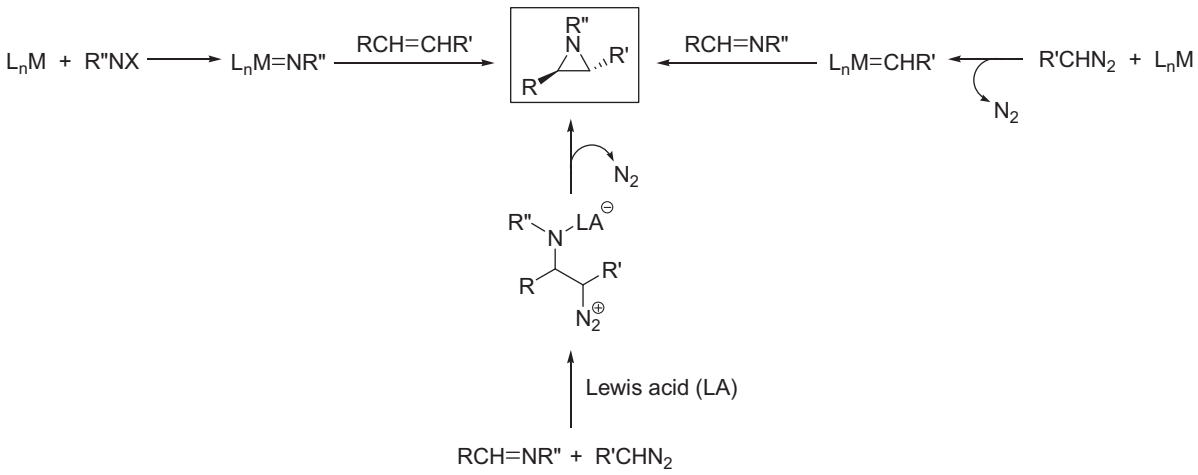
Mitomycin A X= OMe, Y= Me, Z= H
Mitomycin B X= OMe, Y= H, Z= Me
Mitomycin C X= NH_2, Y= Me, Z= H
Porfiromycin X= NH_2, Y= Me, Z= Me



Mitomycin G X= NH_2, Y= Me
Mitomycin H X= OMe, Y= H
Mitomycin K X= OMe, Y= Me

Figure 4.16. *The Mitosanes*

Moreover aziridines are known as very interesting building blocks in organic chemistry comparable to epoxides.[71] In sharp contrast with these epoxides, the methods for asymmetric aziridine formation are scarce. This is due to the fact that the discovery of useful methods for asymmetric aziridination catalysis has proven to be extremely difficult. The transfer of a nitrene group to an olefin, the reaction between diazo esters and imines mediated by either carbene transfer catalysts or Lewis acid catalysts are three fundamentally different approaches to the design of asymmetric catalysts for aziridination (Scheme 4.15). The nitrene transfer to olefins has received the greatest share of attention. Therefore we discuss only this type of catalysis in the following.

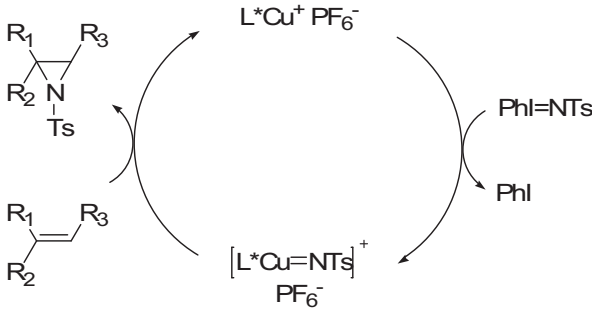


Scheme 4.15. *Three different approaches to the design of asymmetric aziridination catalysts.*

A breakthrough in aziridination catalysis was made by Evans. He used Cu(I)- and Cu(II)-catalysts and (N-(*p*-toluenesulfonyl)imino)phenyliodinane (PhINTs), as a nitrene precursor, for the aziridination of both electron-rich and electron-deficient olefins.[72]

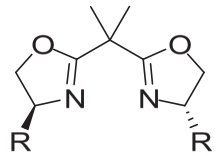
The research of asymmetric aziridination was stimulated by the knowledge about catalytic cyclopropanations and the discovery that metal ions useful for cyclopropanations were also effective in aziridinations. Only a limited number of ligands are effective in the asymmetric Cu-catalyzed aziridination. The two main groups are chiral bisoxazolines and chiral diimine-based ligands (Table 4.12).
Evans *et al.* used a chiral bisoxazoline **4.10a** and **4.10b** with Cu(I)triflate in the aziridination of cinnamate ester derivatives with high enantioselectivities (Table 4.12, entries 1-3).[73] No other substrate classes have been demonstrated to undergo aziridination with synthetically-useful selectivity. The group of Jacobsen optimized chiral 1,2-diimine derivatives, e.g. **4.51** and **4.67** (Table 4.12, entries 4-6).[74] The ligand prepared from 2,6-dichlorobenzaldehyde was the most enantioselective. Again the substrate scope was limited and the highest selectivities were obtained for *cis*-alkenes. Scott *et al.* developed biaryl Schiff base ligand **4.68**. Remarkably, ligand **4.68** gave high enantioselecties in the aziridination of both 6-acyl-2,2-dimethylchromene **4.74** and cinnamate esters (Table 4.12, entries 7-9).[75] Ligand **4.69** showed very low selectivities for styrene but moderate too high for cinnamate esters (Table 4.12, entries 10-12).[76]

A mechanism for the copper-catalyzed asymmetric aziridination was suggested by Jacobsen (Scheme 4.16).[74a] Mechanistical studies provided support for this redox mechanism.

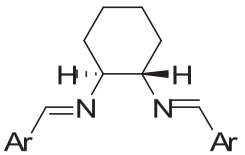


Scheme 4.16. *Redox mechanism for Cu(I)-catalyzed aziridinations of olefines with PhI=NTs.*

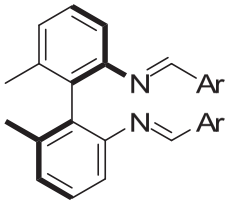
Entry	[Cu]	Ligand	catalyst loading (mol % Cu/ligand)	olefin	4Å molecular sieves	Equiv. PhINTs	solvent, conditions	Yield (%)	% ee	config.
1	CuOTf	**4.10a**	5/6	**4.70**	+	2	C_6H_6, 24h, 21 °C	63	94	(2*R*, 3*S*)
2	CuOTf	**4.10a**	5/6	**4.71**	+	2	C_6H_6, 24h, 21 °C	60	96	(2*R*, 3*S*)
3	CuOTf	**4.10b**	5/6	**4.72**	+	1	styrene, 2.5h, 0 °C	89	63	(*R*)
4	CuOTf	**4.51**	10/11	**4.73**	/	1.5	CH_2Cl_2, -78 °C	75	>98	(3*R*, 4*R*)
5	CuOTf	**4.51**	10/11	**4.72**	/	1.5	CH_2Cl_2, -78 °C	79	66	(*R*)
6	CuOTf	**4.67**	5/5.5	**4.73**	/	1.5	CH_2Cl_2, -78 °C	n.d.	50	(3*R*, 4*R*)
7	$Cu(CH_3CN)_4BF_4$	**4.68**	5/6	**4.70**	/	0.2-1	CH_2Cl_2, rt	70	69	(2*S*, 3*R*)
8	$Cu(CH_3CN)_4BF_4$	**4.68**	5/6	**4.71**	/	0.2-1	CH_2Cl_2, -40 °C	77	89	(2*S*, 3*R*)
9	$Cu(CH_3CN)_4(BF_4)_2$	**4.68**	5/5.5	**4.74**	/	0.2	CH_2Cl_2, -40 °C	87	99	n.d.
10	$Cu(CH_3CN)_4ClO_4$	**4.69**	5/5.5	**4.70**	+	0.2	CH_2Cl_2, -20 °C	90	69	(2*S*, 3*R*)
11	$Cu(CH_3CN)_4ClO_4$	**4.69**	5/5.5	**4.71**	+	0.2	CH_2Cl_2, -20 °C	91	97	(2*S*, 3*R*)
12	$Cu(CH_3CN)_4ClO_4$	**4.69**	5/5.5	**4.72**	+	0.2	CH_2Cl_2, -20 °C	93	25	(*S*)



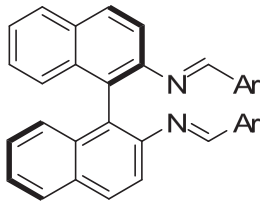
4.10a, (R= Ph)
4.10b, (R= CMe_3)



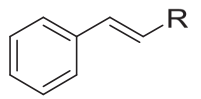
4.51, (Ar= 2,6-$Cl_2C_6H_3$)
4.67, (Ar= C_6H_5)



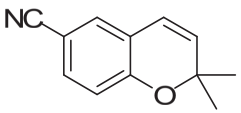
4.68
(Ar= 2,6-$Cl_2C_6H_3$)



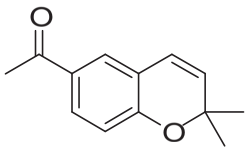
4.69
(Ar= 2,6-$Cl_2C_6H_3$



4.70, R= CO_2Me
4.71, R= CO_2t-Bu
4.72, R= H



4.73



4.74

Table 4.12. *Literature results for the Cu-catalyzed aziridination.*

The newly synthesized imidate ligands (Figure 4.17) were evaluated in the Cu(I) catalyzed aziridination to methylcinnamate **4.70**, *t*-butylcinnamate **4.71** and 2,2-dimethylchromene **4.73**.

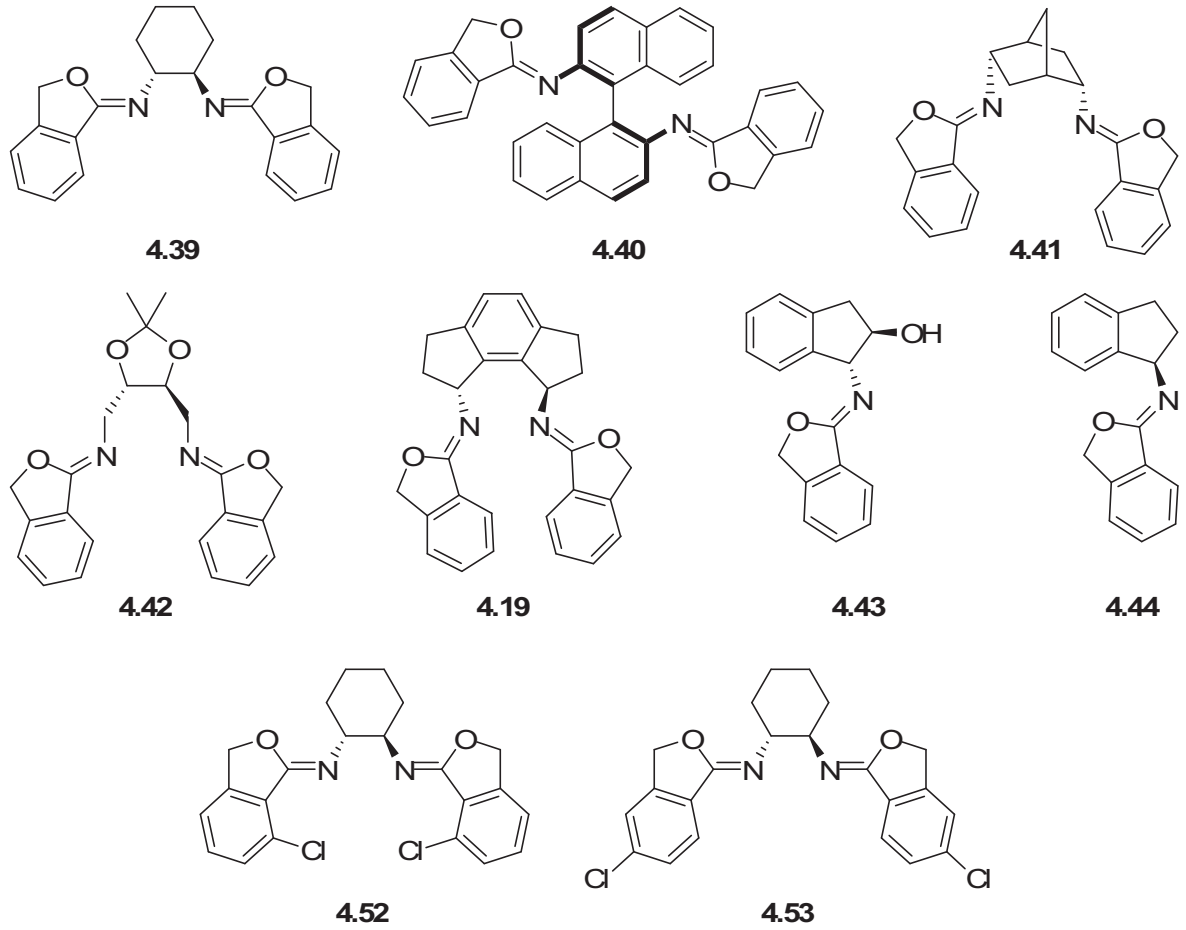
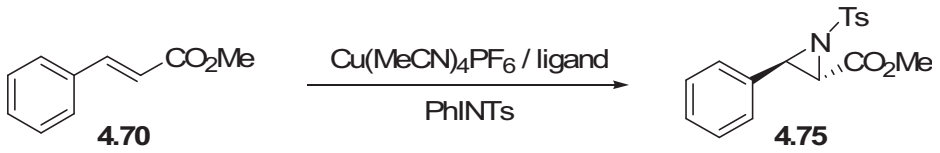


Figure 4.17. *Chiral imidate ligands evaluated in Cu(I)-catalyzed asymmetric aziridination*

We observed excellent yields for all bisimidates (Table 4.13, entries 1 and 3-5) except for imidate **4.40** derived from binaphtyldiamine **4.34** (Table 4.13, entry 2). With imidate alcohol **4.43** and monodentate imidate **4.44** as a chiral ligand, low yields were obtained (Table 4.13, entries 6 and 7). The enantioselectivities were low (Table 4.13, entries 4-7) to moderate (Table 4.13, entries 1-3). Nevertheless, the result obtained with ligand **4.39** was promising (Table 4.13, entry 1.



4.70 **4.75**

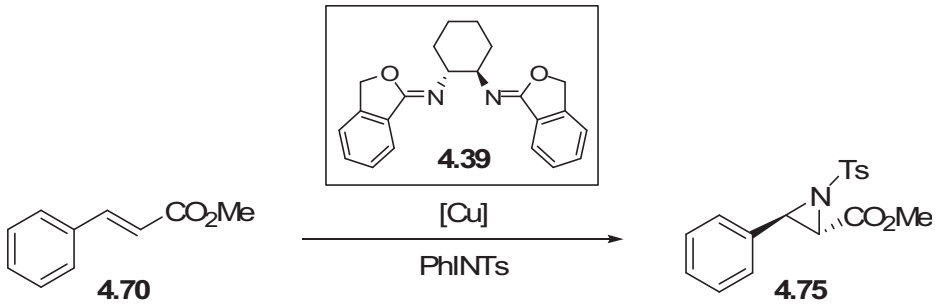
Entry	ligand	Time (h)	Yield (%)[b]	% ee[c]	Configuration[d]
1	**4.39**	22	90	45	2*S*,3*R*
2	**4.40**	21	22	26	2*S*,3*R*
3	**4.41**	22	90	37	2*S*,3*R*
4	**4.42**	23	97	3	n.d.
5	**4.19**	21	87	<1	n.d.
6	**4.43**	24	24	6	2*S*,3*R*
7[e]	**4.44**	21	18	11	2*S*,3*R*

[a] ***Reagents and conditions:*** **4.70** (1 mmol), PhINTs (0.2 mmol), $Cu(MeCN)_4PF_6$ (10 mol%), ligand (11 mol%), 100 mg 4Å molecular sieves, 2.5 mL CH_2Cl_2, T= -40℃.
[b] Yield calculated on PhINTs as limiting reagent.
[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).
[d] Assigned by the sign of the optical rotation.
[e] Because **3g** is a monodentate ligand 22 mol% was used.

Table 4.13. *Cu(I)-catalyzed asymmetric aziridination of methylcinnamate (**4.70**).*

Given the good results obtained with ligand **4.39**, we wanted to investigate the influence of a chlorine on the aromatic ring of the imidate ligand (ligands **4.52** and **4.53**). Ligand **4.52** was synthesized in analogy with the Jacobsen imine ligand **4.51**. While the latter gives an excellent enantioselectivity when chlorine atoms are present in the *ortho* position, our ligand **4.52** gave the target product **4.75** with only a marginal selectivity (4% ee). Ligand **4.53** gave a selectivity of 29% ee.

With ligand **4.39**, we tried to optimize the reaction conditions by varying different reaction parameters (Table 4.14). Changing the copper source resulted in a lower yield and comparable selectivities (Table 4.14, entries 1-3). With a copper (II) species, the reaction was sluggish and almost no conversion was observed (Table 4.14, entry 4). Changing the solvent led to very slow reactions (Table 4.14, entries 5-8). Dichloroethane as a solvent afforded a good yield but lower enantioselectivity than dichloromethane (Table 4.14, entry 9). The highest enantioselectivity was observed at a temperature of -78℃ (51% ee) (Table 4.14, entry 11).

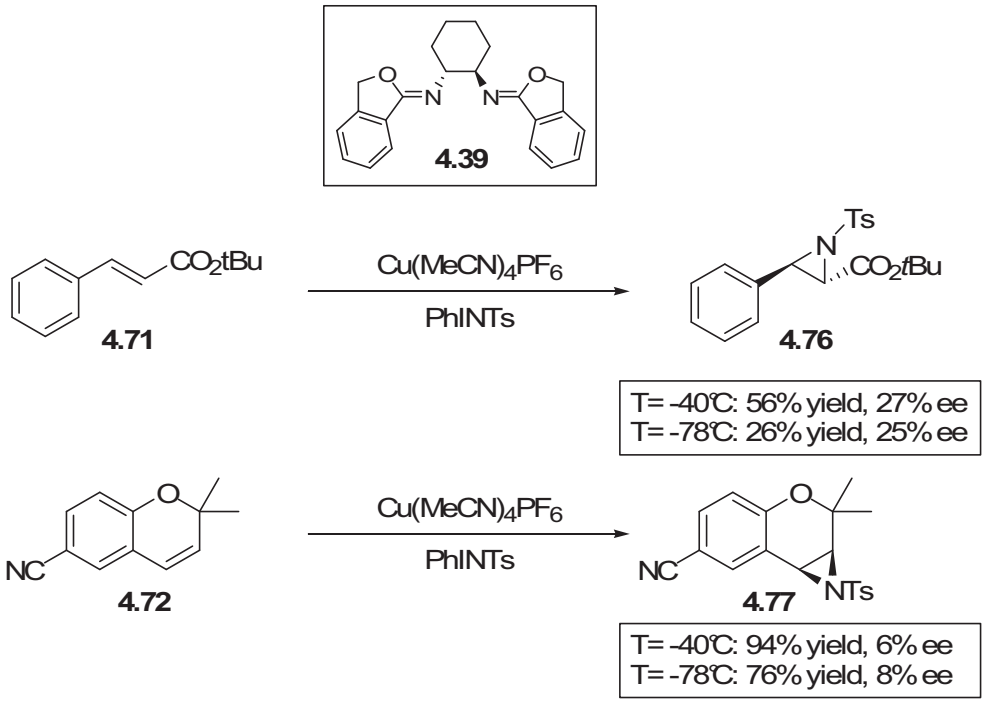


Entry	[Cu]	Solvent	Temp (℃)	Time (h)	Yield (%)[b]	% ee[c]
1	CuOTf	CH_2Cl_2	- 40	24	18	42
2	$Cu(MeCN)_4BF_4$	CH_2Cl_2	- 40	24	24	42
3	$Cu(MeCN)_4OTf$	CH_2Cl_2	- 40	24	44	46
4	$Cu(OTf)_2$	CH_2Cl_2	- 40	24	-	-
5	$Cu(MeCN)_4PF_6$	toluene	- 40	48	< 5	< 1
6	$Cu(MeCN)_4PF_6$	CH_3CN	- 40	24	31	28
7	CuOTf	toluene	- 40	24	-	-
8	CuOTf	benzene	25	24	56	14
9	$Cu(MeCN)_4PF_6$	$(CH_2Cl)_2$	- 30	24	87	33
10	$Cu(MeCN)_4PF_6$	CH_2Cl_2	25	24	64	27
11	$Cu(MeCN)_4PF_6$	CH_2Cl_2	- 78	24	58	51

[a] ***Reagents and conditions:*** **4.70** (1 mmol), PhINTs (0.2 mmol), [Cu] (10 mol%), ligand **4.39** (11 mol%), 100 mg 4Å molecular sieves, 2.5 mL solvent.
[b] Yield calculated on PhINTs as limiting reagent.
[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).

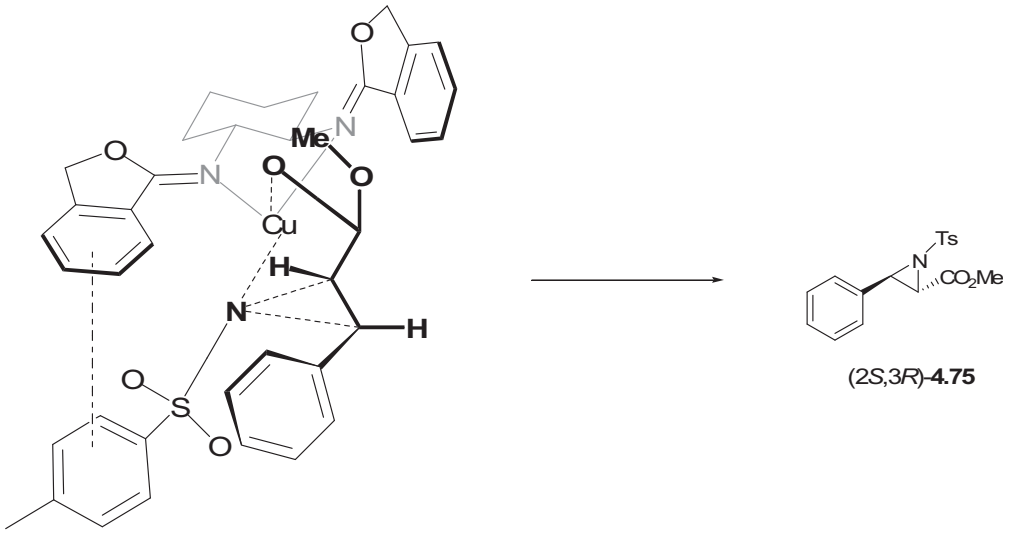
Table 4.14. *Cu(I)-catalyzed asymmetric aziridination of methylcinnamate (**4.70**): Optimization of the reaction parameters with ligand **4.39**.*

To conclude, we tested ligand **4.39** in the Cu(I)-catalyzed asymmetric aziridination of *t*-butylcinnamate **4.71** and 2,2-dimethylchromene **4.73** (scheme 4.17). Aziridination of **4.71** gives a disappointing yield and selectivity. Aziridination of a *cis*-alkene **4.72** resulted in high yields, however, the induced selectivity was very low.



Scheme 4.17. *Cu(I)-catalyzed asymmetric aziridination of t-butylcinnamate (**4.71**) and 2,2-dimethylchromene (**4.72**) with ligand **4.39**.*

The aziridination of a prochiral alkene **4.70** with a nitrene-copper complex can be explained as shown in scheme 4.18.[77] The tosyl group is orientated in such a way that the phenyl can interact via π-stacking with one of the phenyls of the bisimidate ligand. The alignment of the cinnamate ester is now controlled by the chiral ligand via the orientation of the tosyl group. The cinnamate ester is precisely orientated via a two-centre binding with the nitrene-copper complex. The carbonyl oxygen of the CO_2Me group coordinates with the copper and hence a four-coordinate copper species is formed. This results in the formation of the (2*S*,3*R*)-enantiomer and is consistent with our observations.



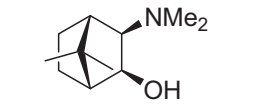
Scheme 4.18. *The stereoselectivity in the Cu(I)-catalyzed aziridination with **4.39** as a ligand.*

4.7.2 Catalytic asymmetric organozinc additions to carbonyl compounds[78,79]

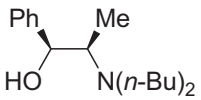
In 1984, Oguni and Omi reported that (*S*)-leucinol catalyzed the reaction of diethylzinc with benzaldehyde with moderate enantioselectivity (49% ee).[80] Since then a large number of chiral catalysts have been developed and high selectivities have been achieved. In addition, the reaction of diethylzinc has become a classical test in the design of new ligands.

Enantioselective alkylation of aldehydes has distinct advantages over enantioselective reduction of ketones: (1) A chiral center is created in combination with an elongation of the carbon chain; (2) In general, higher enatioselectivities are obtained for aliphatic aldehydes via an enantioselective alkylation.

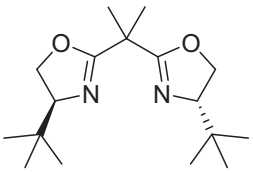
The most successful ligands for this type of transformation are aminoalcohols.[81] Also oxazoline ligands catalyze the reaction with high selectivities. However, bisoxazoline ligands without a hydroxyl functionality induce very low selectivities.[82] Diols, such as TADDOL (**4.81**) and BINOL (**4.82**), in combination with $Ti(^{i}OPr)_4$ are very efficient catalyst systems for the Et_2Zn addition (Figure 4.18).[83,84]



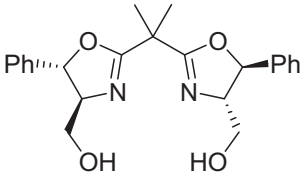
4.78
99% ee



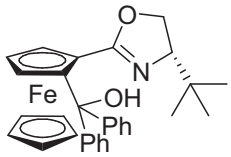
4.79
90% ee



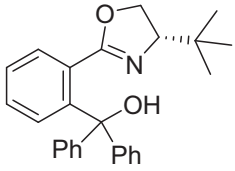
4.10b
20% ee



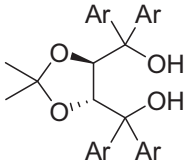
4.80
93% ee



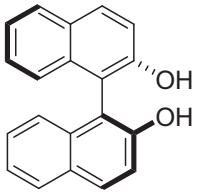
4.56
93% ee



4.57
92% ee



TADDOL (**4.81**)
up to 99% ee



BINOL (**4.82**)
89% ee

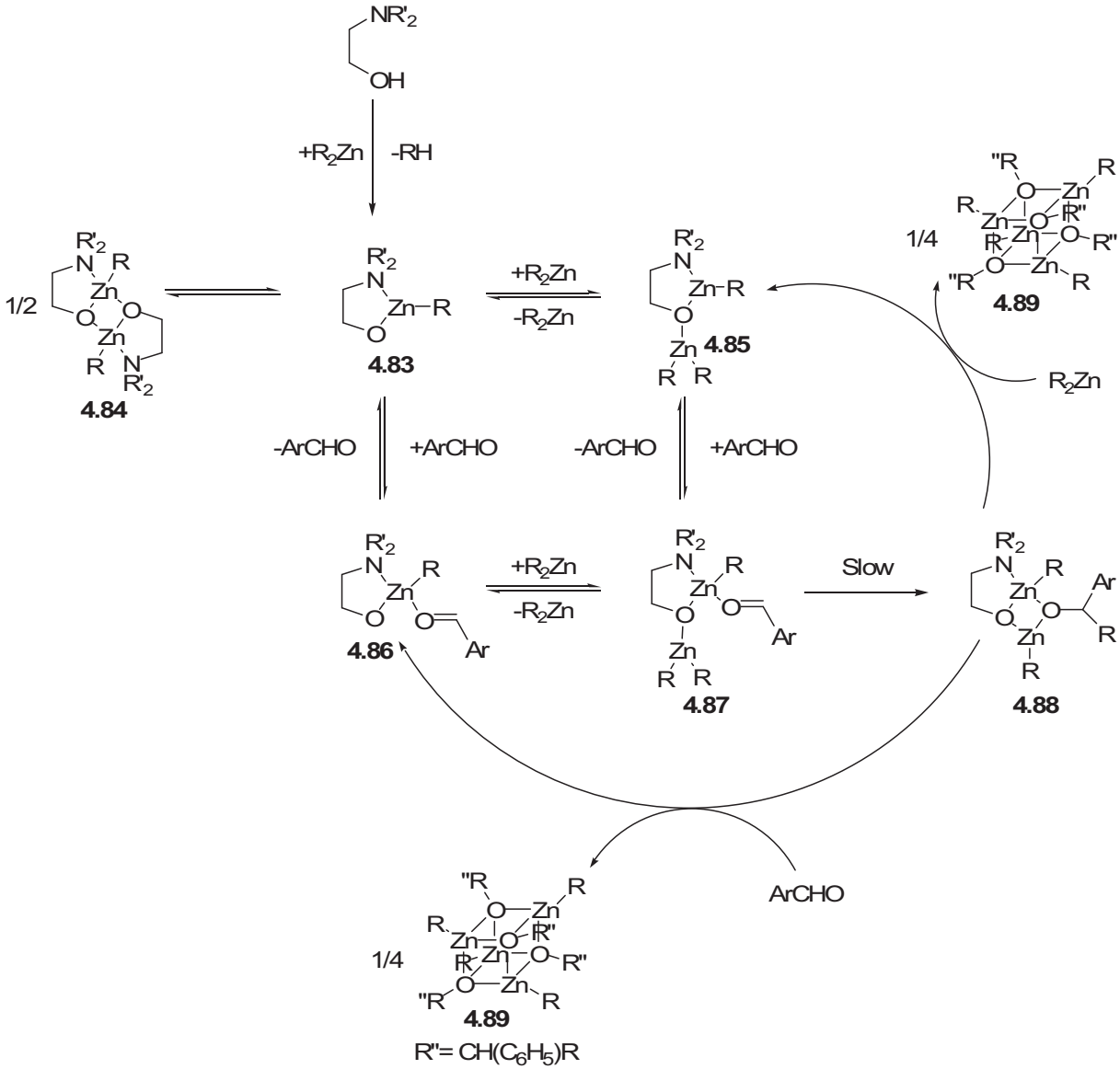
Figure 4.18. *Literature results for the asymmetric diethylzinc addition to benzaldehyde.*

Dialkylzinc reagents do not easily react with aldehydes in the absence of a catalyst because their alkyl metal bond is rather non polar. Addition of a Lewis base activates the dialkylzinc reagent. It increases the polarity of the alkyl-Zn bond which is now

able to react with aldehydes (Figure 4.19). The catalyst not only accelerates the reaction, but, because it is chiral, it also directs the stereochemical outcome.

Fig 4.19. *Activation of dialkylzinc reagents.*

Noyori has suggested a mechanism for the enantioselective addition of dialkylzinc reagents to aldehydes.[85] The aminoalcohol and R_2Zn generate the alkylzinc alkoxide **4.83** which is in equilibrium with the dimer **4.84**. Next, **4.83** reacts with R_2Zn to give **4.85**, which subsequently complexes with benzaldehyde. An intramolecular alkyl-transfer reaction leads to **4.88** and reaction with R_2Zn forms a stable cage tetramer **4.89**. Work-up in water delivers the free alcohol (Scheme 4.19).



Scheme 4.19. *Catalytic Cycle for β-Amino Alcohol Promoted Addition of Dialkylzinc to Aldehydes.*

The synthesized chiral imidate and oxazoline-alcohol ligands were tested in the asymmetric addition of Et_2Zn to aldehydes.

4.7.2.1 Asymmetric 1,2-addition of diethylzinc to benzaldehyde in the presence of chiral imidate ligands.

The bisimidate ligands (**4.19** and **4.39**-**4.44)** were tested in 1,2-additions of diethylzinc to benzaldehyde. We also compared our bisimidate ligands with bisamidine ligands **4.15** and **4.90** (Figure 4.20).[31]

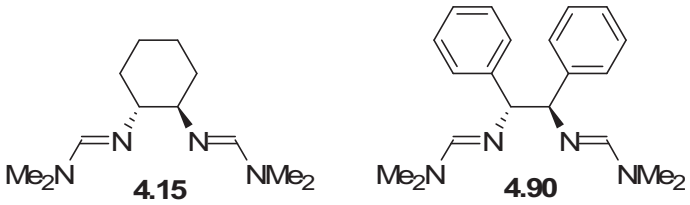
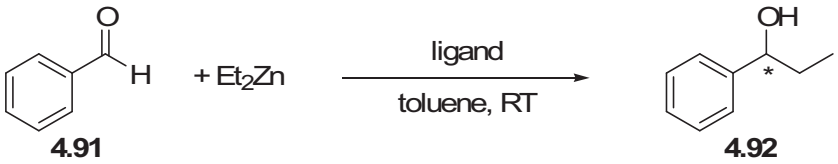


Figure 4.20. *Chiral bisamidine ligands.*

We observed excellent yields with all bisimidate ligands, except for ligand **4.42** and **4.19** (Table 4.15, entries 1-5). The monodentate imidate ligands gave slower reactions (Table 4.15, entries 6-7). Also the bisamidines gave very good yields (Table 4.15, entries 8-9). However the enantioselectivities were in general low for both bisimidates and bisamidines, with one exception: ligand **4.40** afforded the product in good yield and enantioselectivity (83%, 75% ee) (Table 4.15, entry 2). With ligand **4.40**, we tried to optimize the reaction conditions (Table 4.15, entries 10-15). Addition of $Ti(^{i}OPr)_4$ resulted in lower selectivities (Table 4.15, entries 10-12). Decreasing the temperature resulted in a much slower reaction (Table 4.15, entry 13). Increasing the amount of ligand resulted in a selectivity comparable to our first experiment with ligand **4.40** and a slight decrease in yield (Table 4.15, entries 14-15).



4.91 **4.92**

Entry	Ligand	Time (h)	Yield (%)	% ee[b]	Configuration
1	**4.39**	48	80	11	*S*-(-)
2[c]	**4.40**	24	83	75	*R*-(+)
3	**4.41**	24	87	14	*R*-(+)
4	**4.42**	24	38	<1	n.d.
5	**4.19**	24	42	5	*R*-(+)
6	**4.43**	24	14	36	*S*-(-)
7	**4.44**	24	23	4	*R*-(+)
8	**4.15**	24	87	4	*S*-(-)
9	**4.90**	3	95	24	*S*-(-)
10[c,d]	**4.40**	24	87	64	*R*-(+)
11[c,e]	**4.40**	24	73	54	*R*-(+)
12[c,f]	**4.40**	24	77	46	*R*-(+)
13[c,g]	**4.40**	72	18	59	*R*-(+)
14[h]	**4.40**	48	70	75	*R*-(+)
15[g,h]	**4.40**	48	71	76	*R*-(+)

[a] ***Reagents and conditions**:* **4.91** (1 mmol), Et_2Zn (1.5 mmol), ligand (5 mol %), 4 mL toluene, the reaction was performed at room temperature.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).
[c] 2.5 mol % ligand was added.
[d] 2.5 mol % $Ti(^iOPr)_4$ was added.
[e] 20 mol % $Ti(^iOPr)_4$ was added.
[f] 30 mol % $Ti(^iOPr)_4$ was added.
[g] Reaction temperature = 0℃.
[h] 10 mol % of ligand **4.40**.

Table 4.15. *Asymmetric addition of Et_2Zn to benzaldehyde in the presence of chiral imidate and amidine ligands.*

4.7.2.2 Asymmetric 1,2-addition of diethylzinc to benzaldehyde in the presence of chiral imidate- and oxazoline-alcohol ligands.

The synthesized imidate- and oxazoline-alcohol ligands were tested and compared in the asymmetric diethylzinc addition to aldehydes (Figure 4.21).

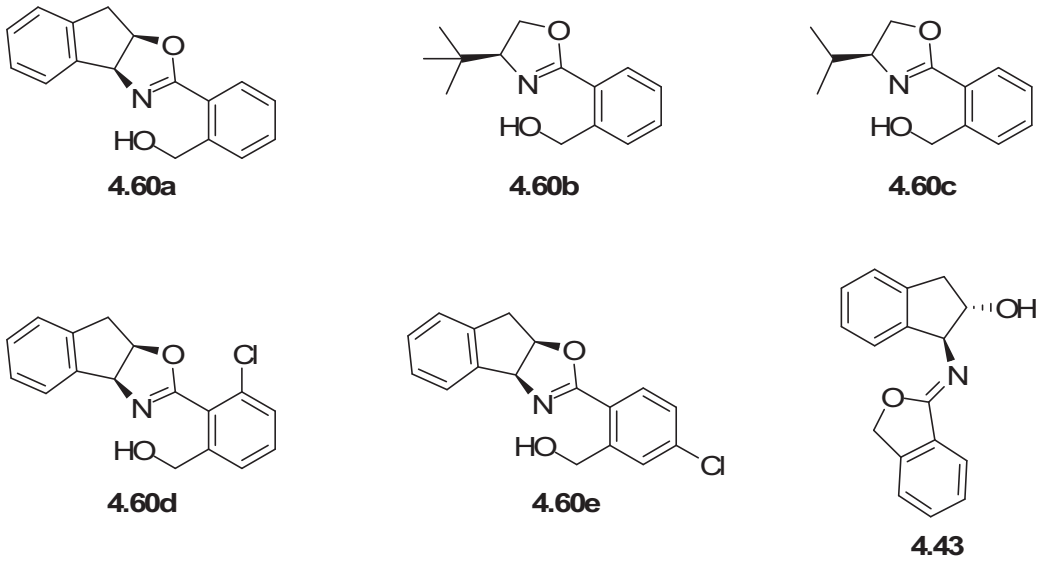
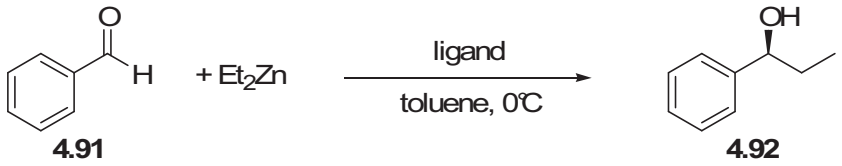


Figure 4.21. *Chiral imidate- and oxazoline- alcohol ligands evaluated in the asymmetric diethylzinc 1,2-addition to aldehydes.*

The best result was obtained with **4.60a** as a chiral ligand (69% yield, 85% ee) (Table 4.16, entry 1). Less bulky groups on the oxazoline ring result in a lower selectivity (Table 4.16, entries 2-3). When performed with the imidate alcohol **4.43** as a chiral ligand, the reaction was sluggish and a low enantioselectivity was observed (Table 4.16, entry 4). Surprisingly, when the reaction was performed with ligand **4.60d**, containing a chlorine substituent in the *ortho*-position, **4.91** was obtained in a low yield and enantioselectivity (Table 4.16, entry 5). In contrast, ligand **4.60e**, bearing a chlorine in the *para*-position of the oxazoline substituent, afforded a yield and selectivity which were only slightly lower than with **4.60a** (Table 4.16, entry 6).



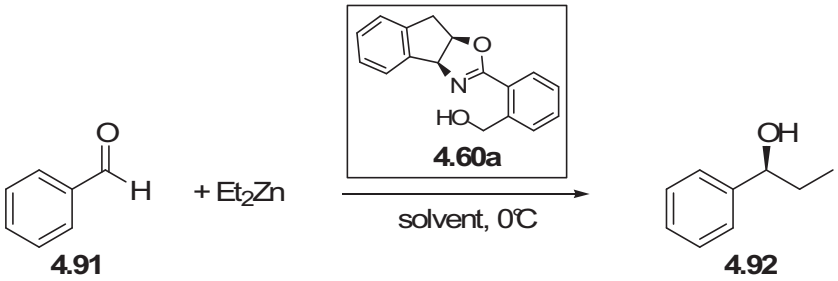
4.91 **4.92**

Entry	Ligand	Time (h)	Yield (%)	% ee[b]	Configuration[c]
1	**4.60a**	48	69	85	*S*-(-)
2	**4.60b**	48	31	55	*S*-(-)
3	**4.60c**	48	60	44	*S*-(-)
4[d]	**4.43**	24	14	36	*S*-(-)
5	**4.60d**	48	25	15	*S*-(-)
6	**4.60e**	48	66	79	*S*-(-)

[a] ***Reagents and conditions**:* **4.91** (0.5 mmol), Et_2Zn (0.75 mmol), ligand (10 mol %), 2 mL toluene, T = 0℃.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).
[c] Assigned by the sign of the optical rotation.
[d] Reaction performed at room temperature

Table 4.16. *Asymmetric additions of Et_2Zn to benzaldehyde in the presence of chiral imidate- and oxazoline-alcohol ligands.*

With **4.60a** as our best ligand, we tried to optimize the reaction parameters (Table 4.17). Addition of $Ti(^iOPr)_4$ resulted in a higher yield but a lower selectivity (Table 4.17, entry 2). In the presence of $Ti(^iOPr)_4$ and *n*-BuLi, the reaction was rather unselective (Table 4.17, entry 3). When the reaction was performed with only *n*-BuLi to deprotonate the ligand, the yield and selectivity did not improve (Table 4.17, entry 4). Varying the solvent had no beneficial effect compared to our initial experiment (Table 4.17, entries 1 and 5-8).



Entry	Solvent	Additive[b]	Yield (%)	%ee[c]
1	toluene	/	69	85
2	toluene	$Ti(^iOPr)_4$	82	55
3	toluene	$Ti(^iOPr)_4$ / *n*-BuLi	57	9
4	toluene	*n*-BuLi	46	63
5	*n*-hexane	/	13	29
6	CH_2Cl_2	/	36	73
7	THF	/	9	81
8	Et_2O	/	58	84

[a] ***Reagents and conditions**:* **4.91** (0.5 mmol), Et_2Zn (0.75 mmol), ligand (10 mol %), 2 mL toluene, T= 0°C.
[b] The additives were added in an equimolar amount in comparison to the ligand.
[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).

***Table 4.17.** Asymmetric additions of Et_2Zn to benzaldehyde in the presence of **4.60a** as a chiral ligand: Optimization of the reaction parameters.*

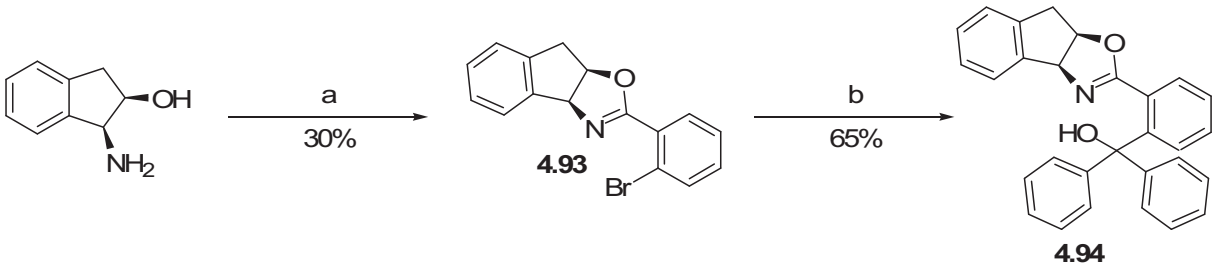
Next, a variety of substituted arylaldehydes was applied (Table 4.18). In general, lower yields and selectivities were obtained in comparison with the unsubstituted benzaldehyde. The best result was obtained with 2-naphtaldehyde (Table 4.18, entry 4).

Entry	Benzaldehyde	Yield (%)	% ee[a]	configuration[b]
1	2-Cl-benzaldehyde	57	55	*S*-(-)
2	3-Cl-benzaldehyde	46	74	*S*-(-)
3	4-Cl-benzaldehyde	24	62	*S*-(-)
4	2-naphtaldehyde	52	87	*S*-(-)
5	*trans*-cinnamaldehyde	32	61	*S*-(-)

[a] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H, AD-H, OB-H).
[b] Assigned by the sign of the optical rotation.

***Table 4.18.** Asymmetric addition of Et_2Zn to several substituted aldehydes in the presence of **4.60a** as a chiral ligand.*

Remarkably, while with (*S*)-**4.60b** as the ligand we obtained (*S*)-**4.92** with an ee of 55% (Table 4.16, entry 2), with the related (*S*)-**4.57** as a ligand Bolm *et al*. reported formation of the opposite enantiomer (*R*)-**4.92** in 92% ee.[61] In order to verify if this chirality switch also holds for other ligands, we synthesized (1*S*,2*R*)-**4.94** as an analogue of (1*S*,2*R*)-**4.60a** with a CPh_2-tether (Scheme 4.20). When the diethylzinc addition was performed in the presence of **4.94**, indeed the opposite enantiomer (*R*)-(**4.92**) was obtained in 86% yield, but in only 22% ee.



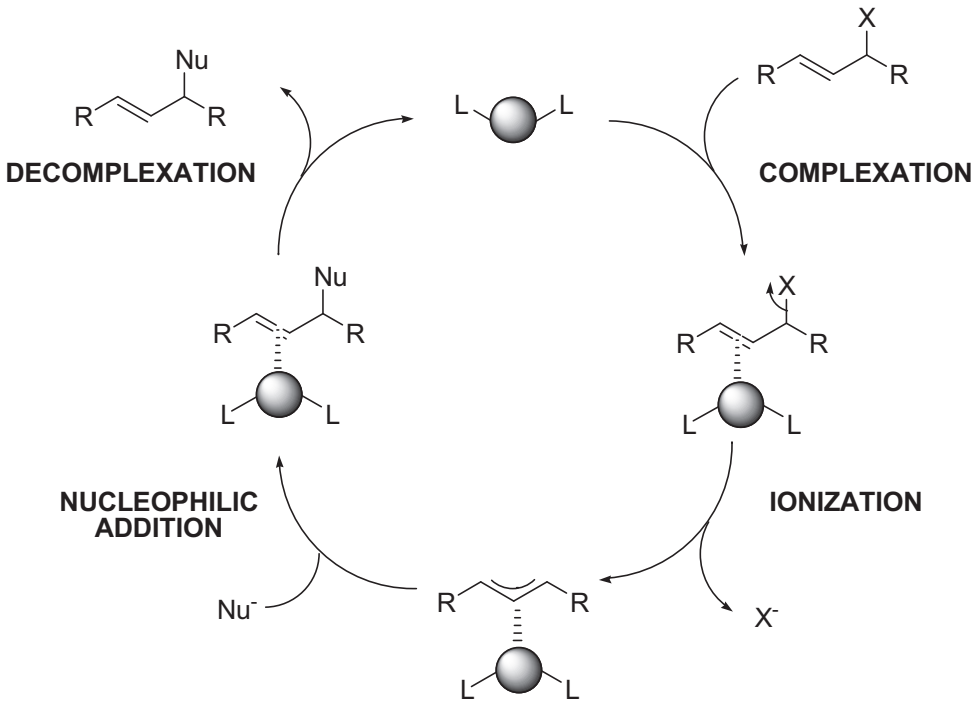
Scheme 4.20. *Synthesis of the analogue of* ***4.60a*** *with a CPh_2-connection: (a) 2-bromobenzonitrile (1 equiv), anhydrous $ZnCl_2$ (5 mol %), anhydrous chlorobenzene, $T_{reflux.}$ (b) (i) n-BuLi (1.1 equiv), Et_2O, -78℃. (ii) benzophenone (1.15 equiv), -40℃ to RT overnight.*

Clearly, this chirality switch is caused by the presence of the two phenyl substituents, as the absolute configuration of the ligand remained unchanged. Similar effects have been reported in other papers and are known as "dual stereocontrol".[86,87] Furthermore, in the case of the indane-fused oxazolines **4.60a** and **4.94**, increasing the steric bulk of the tether resulted in a lower enantioselectivity. In contrast, when the chiral substituent on the oxazoline moiety was a *t*-butyl-substituent, higher enantioselectivities were obtained with a bulky phenyl-substituted tether.[61] This effect, together with the dual stereocontrol, suggests that the introduction of the phenyl substituents modifies the catalytic mechanism or the structure of the catalytic site.[86,87]

4.7.3 Asymmetric palladium-catalyzed allylic substitutions[88]

Transition metal-catalyzed allylic substitutions are highly versatile reactions. A wide variety of transition metal complexes derived from palladium[88], iridium[89], nickel[90], ruthenium[91], rhodium[92], molybdenum[93], copper[94], platinum[95] and other elements are known to catalyze allylic substitutions. However, the most widely used transition metal for this purpose is palladium. In 1977, Trost *et al.* were the first to report an example of an enantioselective metal-catalyzed allylic substitution.[96] Since their pioneering work, a lot of effort has been devoted to develop practically useful enantioselective catalysts for this type or reaction.

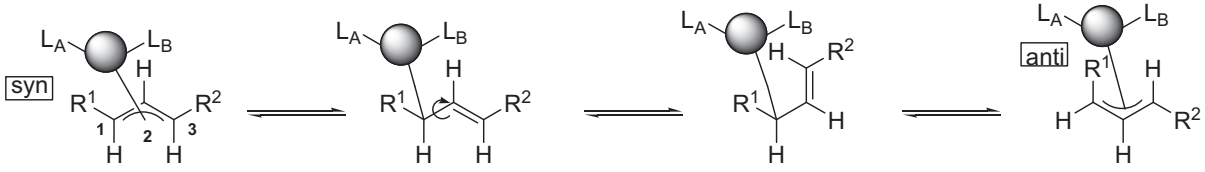
The mechanism of the palladium-catalyzed allylic substitution is generally believed to involve four fundamental steps (Scheme 4.21). The key intermediate of the catalytic cycle is a (π-allyl)metal complex. Depending on the structure of the substrate, every step provides an opportunity for enantioselection, except for the decomplexation. The addition of a nucleophile involves two pathways in which the nature of the nucleophile leads to different stereochemical consequences. Soft nucleophiles (derived from conjugate acids with $pK_a < 25$) usually add to the allyl moiety from the opposite side of the metal. Hard nucleophiles first coordinate to the metal centre and are then transferred intramolecularly to the allyl ligand. The most commonly used nucleophiles are the soft nucleophiles, such as stabilized carbanions or amines. As a consequence, both bond-breaking and bond-forming occurs on the π-allyl face opposite the metal and its chiral ligand. Thus, efficient chirality transfer over the allyl barrier is key to a successful strategy for asymmetric allylic substitutions.



Scheme 4.21. *Catalytic cycle of transition metal catalyzed allylic alkylation.*

The (π-allyl)metal complexes exist in a dynamic equilibrium under typical substitution reaction conditions during which their conformation and geometry may change by intramolecular processes as well as by reversible ligand-dissociation an reassociation processes. There are three important cases: (1) π-σ-π (η^3-η^1-η^3) isomerization; (2) apparent allyl rotation; (3) palladium(0)-catalyzed allyl exchange.

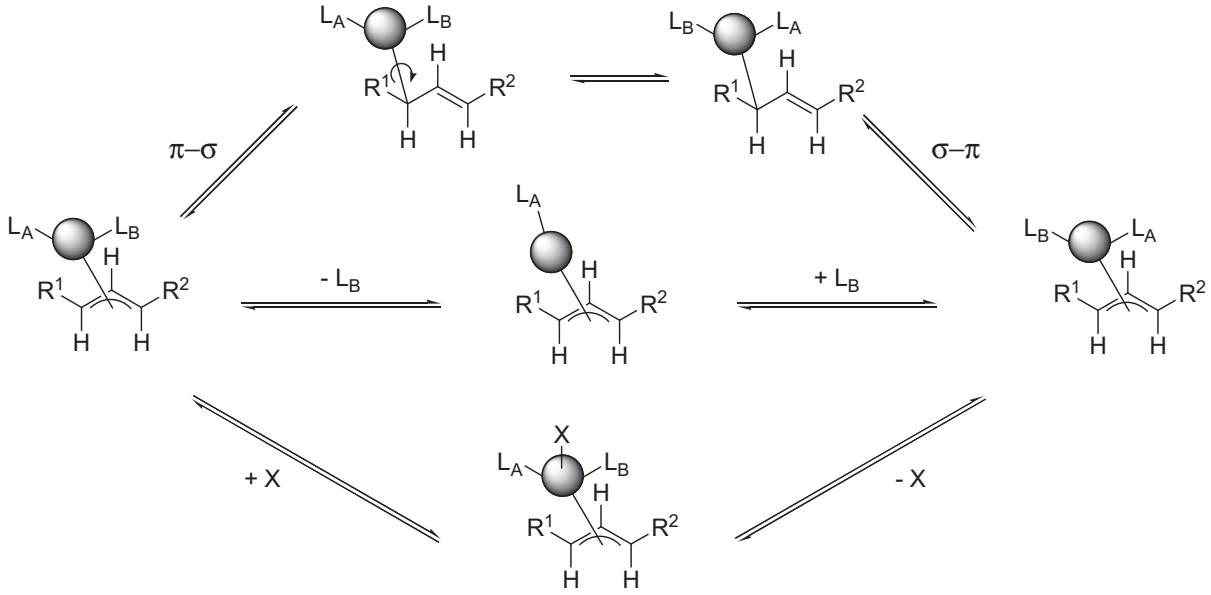
(1) π-σ-π (η^3-η^1-η^3) isomerization involves the rotation around the carbon-carbon bond in the allyl unit. This leads to the *syn*/*anti* interconversion as illustrated in scheme 4.22. (*syn* and *anti* refers to the positions *syn* and *anti* to the substituent at C2) In general, the thermodynamic equilibrium lies far on the side of the *syn*-isomer and only if a substituent is sufficiently small is the *anti*-isomer present in notable amounts.



Scheme 4.22. *Syn/anti isomerization by a η^3-η^1-η^3 mechanism.*

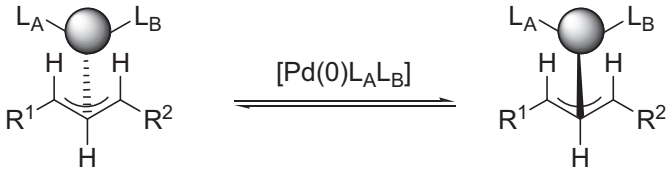
(2) In the apparent allyl rotation process both termini of the allyl system switch position with respect to the other two coordination sites (Scheme 4.23). If the two ligands (L_A and L_B) are different and chiral, this isomerization leads to a diastereoisomeric complex even if the allyl system has structurally identical termini. However, when the two ligands (L_A and L_B) are identical, allyl rotation has no consequences.

There are three possible mechanisms for apparent allyl rotation. The first one involves a π-σ-π (η^3-η^1-η^3) isomerization with concomitant rotation around the Pd-C bond in the η^1-intermediate. A second pathway involves a dissociation of one of the ligands (L_A or L_B). A third possibility is the addition of an external ligand, e.g. halides or polar solvents (DMSO, CH_3CN), to give a pseudo-square-planar allyl-Pd complex which leads to a 'pentacoordinated' complex that undergoes geometrical changes in which the two ligands (L_A and L_B) can switch positions.



Scheme 4.23. *Mechanisms for apparent allyl rotation.*

(3) Isomerization of a π-allyl species can also arise from a bimolecular reaction as shown in scheme 4.24. The Pd(0) complex adds to the free π-face of the allyl ligand and displaces the Pd(II) complex on the backside. This process results in an inversion of the configuration of the π-allyl complex. However, because the concentration of palladium is much lower than the concentration of the substrate and the nucleophile, this type of isomerization is very rare.

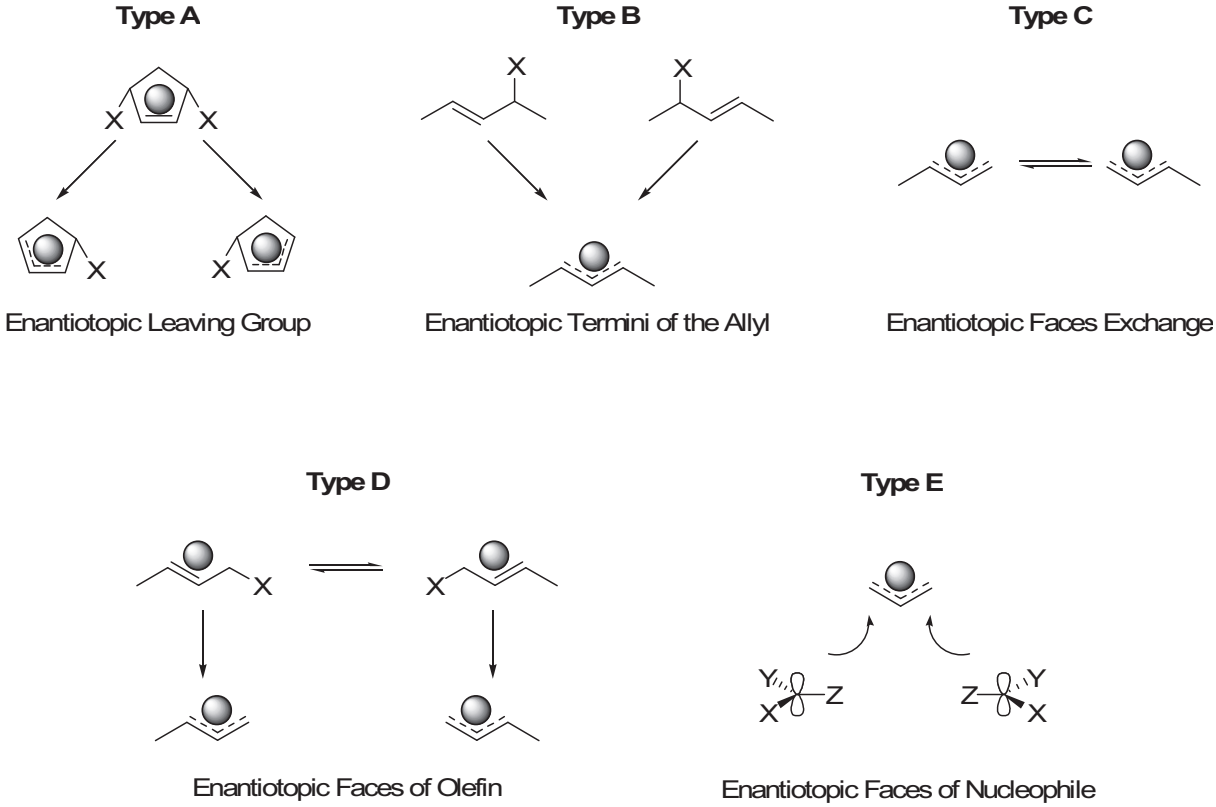


Scheme 4.24. *Palladium(0)-catalyzed allyl exchange.*

A unique feature of these transition metal-catalyzed allylic substitutions is the wide variety of substrates that can be addressed. These substrates can be divided in several classes according to their substitution pattern and the nature of the corresponding allyl-metal complexes (scheme 4.25). In type A substrates there is a discrimination between two enantiotopic leaving groups. In type B, the two enantiomers of a racemic substrate form a *meso*-π-allyl complex wherein a preferential attack of the nucleophile at one of the two allylic termini leads to

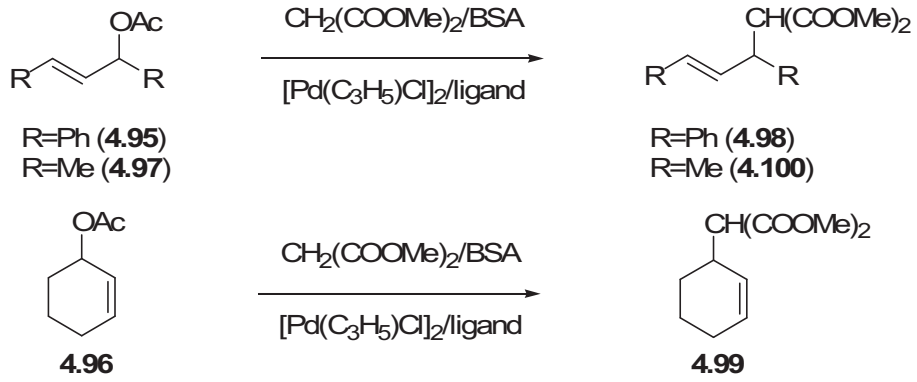
asymmetric induction. This process is a dynamic kinetic enantioselective transformation. The third requires the differentiation between two enantiotopic transition states (type C). Next, the transition metal can complex with one of the two enantiotopic faces of the alkene (type D). Finally, there can be an enantiodiscrimination between the two enantiotopic sides of a prochiral nucleophile (type E).

In the following, we will focus our research on the asymmetric allylic substitution of type B substrates.



Scheme 4.25. *Various sources of enantiodiscrimination in asymmetric allylic substitution.*

Since the pioneering work of Trost *et al.*[96,97], a lot of effort has been devoted by several groups into the design of chiral catalysts. However, the great majority of the catalytic systems developed to date have a rather limited substrate scope (Table 4.19, entries 1, 3-7). Catalysts which have a wider scope are very scarce (Table 4.19, entries 2, 8-11). Typically, high enantioselectivities are obtained for linear hindered substrates and low enantioselectivities for linear unhindered and cyclic substrates, or vice versa. Therefore, the development of enantioselective catalysts which show high enantioselectivities in both substrate classes remains a major challenge.



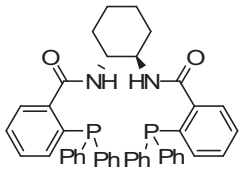
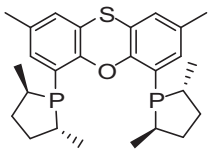
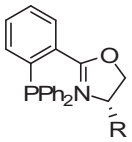
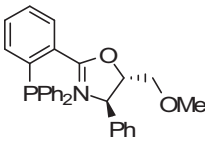
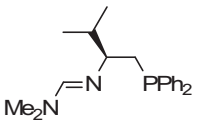
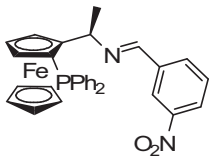
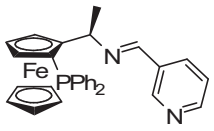
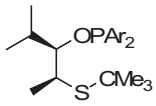
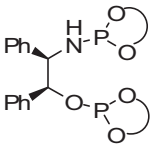
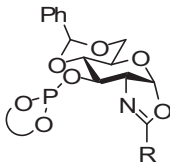
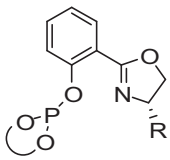
Entry	Ligand	**4.98**	**4.99**	**4.100**	References
1		9% yield 52% ee	86% yield 96% ee	98% yield 92% ee	97a-b
2		- 97% ee	- 93% ee	- 82% ee	98
3		100% yield 99% ee	- 0% ee	96% yield 71% ee	99
4		>99% conversion 96% ee	40% conversion 56% ee	87% conversion 43% ee	100
5		98% yield 95% ee	trace 62% ee	36% yield 59% ee	31

Table 4.19. *Summary of the literature results for the most representative ligands developed for the Pd-(0)-catalyzed allylic substitution reactions.*

6		99% yield 94% ee	81% yield 83% ee	-	101
7		95% yield 98% ee	69% yield 73% ee	-	102
8		28% yield 91% ee	94% yield 91% ee	-	103
9[a]		100% conversion 96% ee	- 81% ee	- 82% ee	104
10[a]		100% conversion 92% ee	100% conversion 75% ee	- 81% ee	105
11[a]		100% conversion >99% ee	100 91% ee	100 73% ee	106

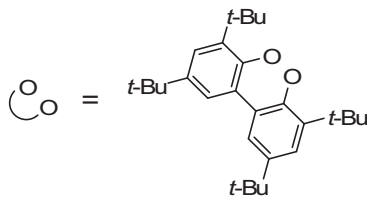
[a] 

Table 4.19-sequel. *Summary of the literature results for the most representative ligands developed for the Pd-(0)-catalyzed allylic substitution reactions.*

We tested our ligands in the palladium-catalyzed asymmetric allylic substitution (Figure 4.22). Our investigation was started with the allylic substitution of 1,3-diphenyl-2-propenyl acetate **4.101** with dimethylmalonate which is regarded as a standard test reaction for evaluating enantioselective catalysts (Table 4.20).

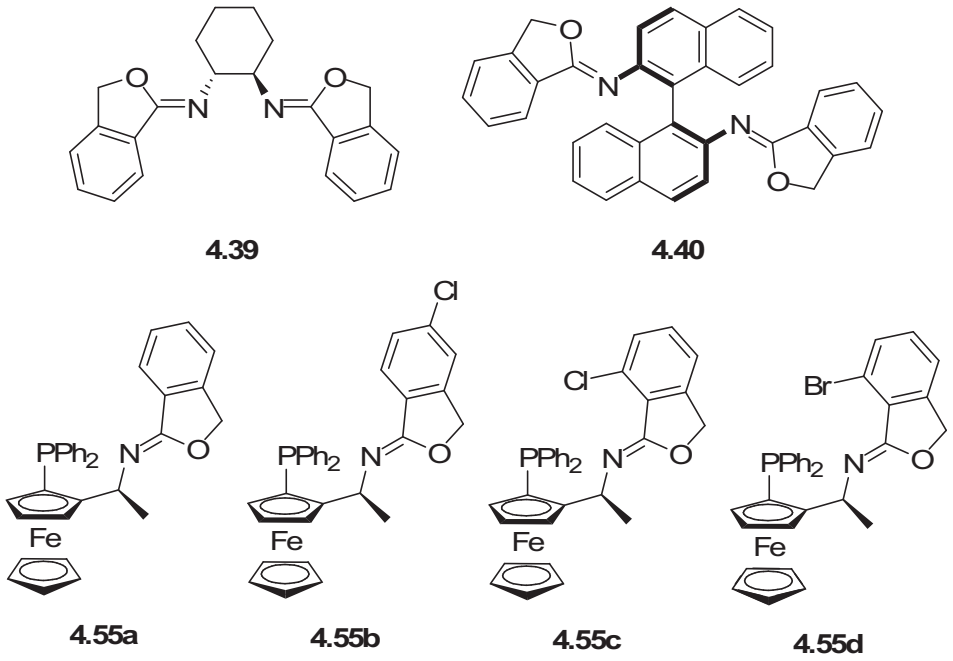
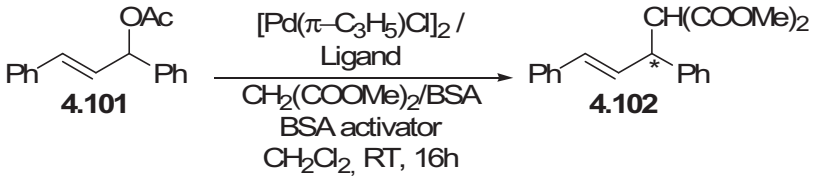


Figure 4.22. *Chiral bisimidate and chiral hybrid imidate-phosphane ligands evaluated in the asymmetric allylic alkylation.*

Bisimidate ligand **4.39** gave no conversion while ligand **4.40** resulted in a moderate yield but an excellent enantioselectivity (Table 4.20, entries 1-2). High yields and excellent enantioselectivities were obtained with all imidate-phosphane ligands (Table 4.20, entries 3-6). The best result was obtained with ligand **4.55b** (Table 4.20, entry 4). We observed also a pronounced BSA-activator effect (Table 4.20, entries 7-9). The enantioselectivity could be further improved when NaOAc was used (Table 4.20, entry 7). With KOAc and CsOAc as a BSA-activator, almost perfect enantioselectivities and reactivities were obtained (Table 4.20, entries 8-9).

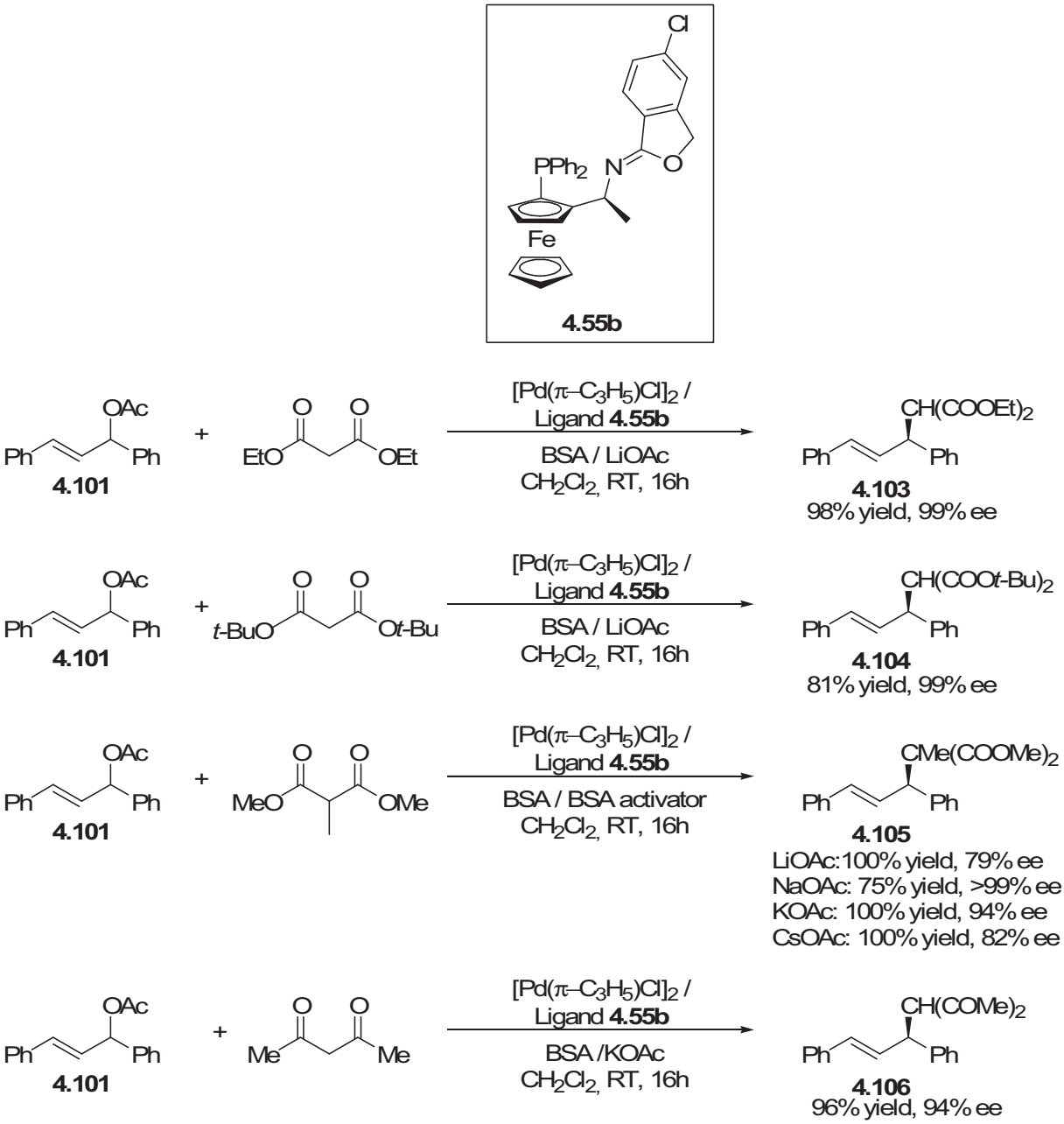


Entry	Ligand	BSA-activator	Yield (%)	% ee[b]	Configuration[c]
1	**4.39**	LiOAc	n.c.[d]	-	-
2	**4.40**	LiOAc	53	95	*R*
3	**4.55a**	LiOAc	82	94	*S*
4	**4.55b**	LiOAc	85	96	*S*
5	**4.55c**	LiOAc	84	96	*S*
6	**4.55d**	LiOAc	85	96	*S*
7	**4.55b**	NaOAc	93	99	*S*
8	**4.55b**	KOAc	99	99	*S*
9	**4.55b**	CsOAc	99	99	*S*

[a] ***Reagents and conditions**:* **4.101** (0.22 mmol), dimethylmalonate (0.66 mmol), BSA (0.66 mmol), BSA activator (10.6 μmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5.5 μmol), ligand (21.8 μmol), CH_2Cl_2 (2 mL), room temperature, 16h.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel AD-H).
[c] Assigned by the sign of the optical rotation.
[d] n.c.: no conversion was observed.

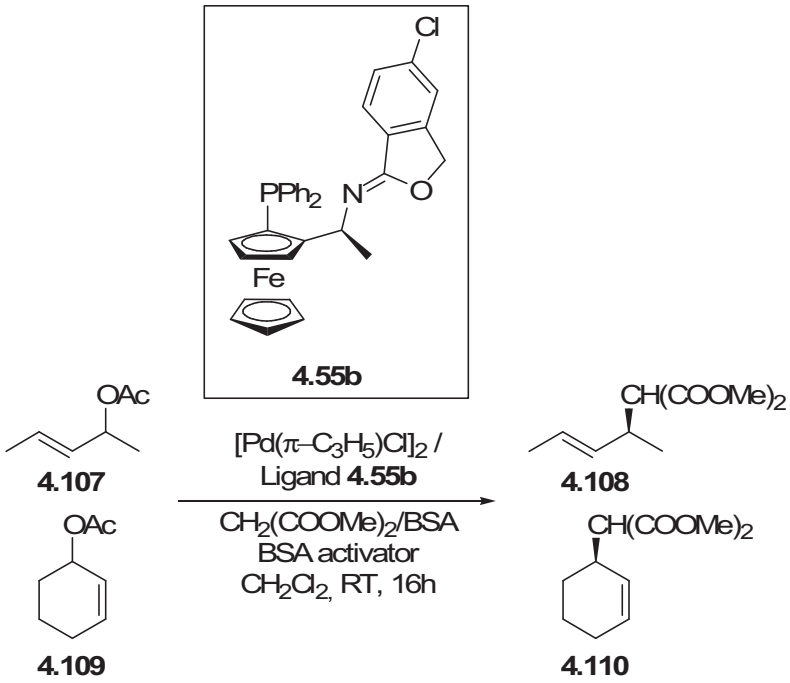
Table 4.20. *Pd-catalyzed allylic alkylation of **4.101** with dimethylmalonate using bisimidate ligands **4.39**-**4.40** and imidate-phosphane ligands **4.55a-d**.*

To further study the potential of these readily available ligands, other nucleophiles were tested (Scheme 4.26). When the reaction was performed with bulky malonates, excellent yields and selectivities were obtained for the corresponding adducts **4.103** and **4.104**. Use of dimethylmethylmalonate as a nucleophile and LiOAc as a BSA activator led to **4.105** in excellent yield and good enantioselectivity. By variation of the BSA activator, the enantioselectivity could be further improved to >99% ee with NaOAc. Also acetylacetone was an effective nucleophile for the palladium-catalyzed allylic alkylation reaction: adduct **4.106** was formed in 96% yield and with an enantioselectivity of 94% ee.



Scheme 4.26. *Allylic substitution reactions with various carbon nucleophiles using **4.55b** as an imidate-phosphane ligand.*

Encouraged by the excellent performance of our new imidate-phosphane ligand **4.55b**, we studied its potential in the allylic alkylation of cyclic substrate **4.107** and unhindered linear substrate **4.109**. Although highly selective catalyst systems have been developed for these substrates, they generally exhibit low enantiocontrol in more hindered substrates, such as substrate **4.101**. Remarkably, also for the unhindered substrate **4.107** good enantioselectivities were observed with our catalyst system (Table 4.21, entries 1-5). The best result was obtained when NaOAc was used as a BSA activator (Table 4.21, entry 4). For the cyclic substrate **4.109**, good enantioselectivities were obtained with all BSA activators in varying yields (Table 4.21, entries 6-9). The best results were obtained with KOAc: a high yield was combined with a good enantioselectivity (Table 4.21, entry 7).



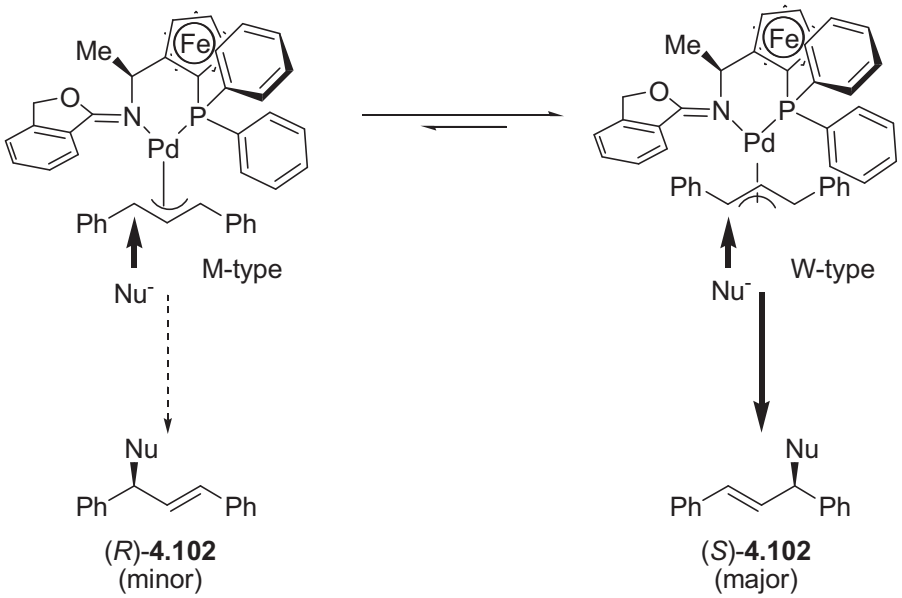
Entry	Substrate	BSA-activator	Yield (%)	% ee[b]	Configuration[c]
1	**4.107**	LiOAc	79	78	*S*
2[d]	**4.107**	LiOAc	23	80	*S*
3	**4.107**	KOAc	86	59	*S*
4	**4.107**	NaOAc	91	83	*S*
5	**4.107**	CsOAc	80	65	*S*
6	**4.109**	LiOAc	49	74	*R*
7	**4.109**	KOAc	76	74	*R*
8	**4.109**	NaOAc	31	73	*R*
9	**4.109**	CsOAc	61	73	*R*

[a] ***Reagents and conditions***: **4.107** or **4.109** (0.22 mmol), dimethylmalonate (0.66 mmol), BSA (0.66 mmol), BSA activator (10.6 µmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5.5 µmol), ligand (21.8 µmol), CH_2Cl_2 (2 mL), room temperature, 16h.
[b] Determined by ^1H NMR analysis by using (+) $Eu(hfc)_3$.
[c] Assigned by the sign of the optical rotation.
[d] The reaction was performed at 0℃.

Table 4.21. *Pd-catalyzed allylic alkylation of **4.107** or **4.109** with dimethylmalonate using imidate-phosphane ligand **4.55b**.*

A mechanistic rationalization of the enantioselectivity observed with non-symmetrical ligands, such as imidate-phosphane ligand **4.55b**, is often difficult and is mostly based on X-ray analyses[107] or extensive NMR studies[108,109]. Unfortunately, attempts to grow a suitable crystal for X-ray analysis of the palladium-complexed ligand **4.55b** all failed.[110] However, a plausible explanation can be rationalized as depicted in scheme 4.27. The allylic moiety can adopt two possible conformations, i.e. an M-shaped conformation or a W-shaped conformation. Computational studies[111] and NMR investigations[112] provide strong evidence that a nucleophile preferentially attacks the allylic carbon terminus *trans* to the phosphorus atom. Based on these data and the observed *S*-configuration of the product, we believe that the major

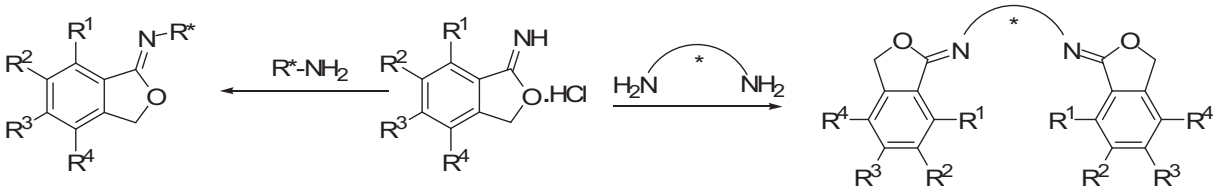
enantiomer is derived from the nucleophilic attack *trans* to the phosphorus centre of the W-shaped π-allyl complex.



Scheme 4.27. *The stereoselectivity observed in the palladium-catalyzed asymmetric allylic alkylation with imidate-phosphane ligand* ***4.55b****.*

4.8 CONCLUSIONS

In summary, we introduced chiral imidates as a new class of chiral ligands. These ligands could be readily obtained via an efficient one-step synthesis starting from imidates and chiral amines (scheme 4.28).

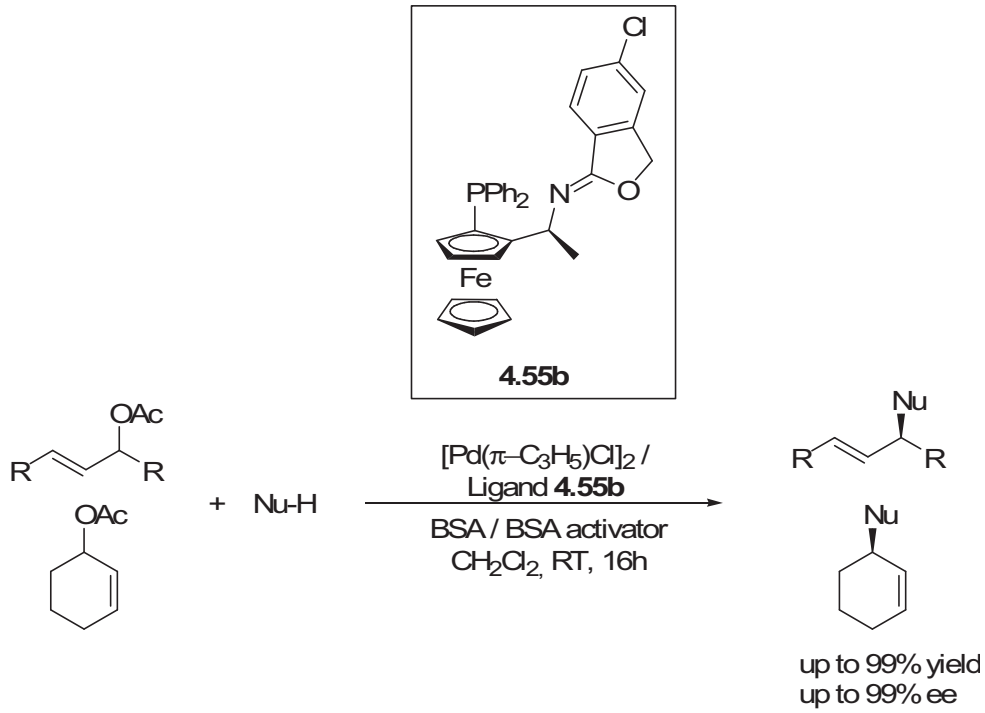


Scheme 4.28. *Synthesis of substituted imidate ligands.*

These monodentate and bidentate ligands were tested in copper(I)-catalyzed asymmetric aziridinations (up to 97% yield and 51% ee) and asymmetric additions of Et_2Zn to benzaldehyde (up to 87% yield and 76% ee). The best result was obtained in the palladium-catalyzed asymmetric allylic alkylation. Although the yield was only 53%, an excellent enantioselectivity was observed (95% ee).

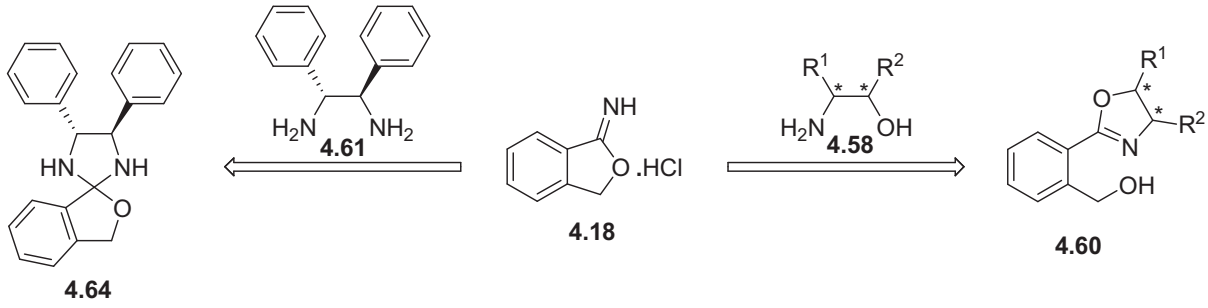
In addition, we synthesized hybrid imidate-phosphane ligands. These ligands were demonstrated to be highly valuable in palladium-catalyzed allylic substitution reactions (Scheme 4.29). Excellent performance of this catalyst system was observed in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with various nucleophiles (up to 99% yield and >99% ee). Moreover, the allylic alkylation of linear unhindered and cyclic substrates resulted in good conversions and

enantioselectivities. Rarely are enantioselective catalysts successful in both substrate classes. Therefore, this imidate-phosphane ligand family can compete with a few other ligands which also provide high selectivities for both hindered and unhindered substrates.



Scheme 4.29. *Pd-catalyzed asymmetric allylic alkylation with hybrid imidate-phosphane ligand* ***4.55b****.*

The cyclic imidate ligand precursor **4.18** could also be used efficiently as a synthetic intermediate for the synthesis of chiral oxazoline alcohol ligands **4.60** and the synthesis of chiral imidazolidines **4.64**. The chiral oxazoline alcohol ligands **4.60** were tested in asymmetric diethylzinc additions to benzaldehydes. Enantioselectivities up to 87% ee were obtained (Scheme 4.30).



Scheme 4.30. *Synthetic applications of cyclic imidate esters.*

In conclusion, we can state that these chiral imidate ligands can evolve into an interesting new type of chiral nitrogen-containing ligands. We have demonstrated that these ligands are easy accessible in one step starting from imidate building blocks (**4.18** and **4.49a-c**). Their accessibility is an important advantage in the design of these new ligands. Some interesting results in catalytic asymmetric test reactions

have been presented in this chapter. However, in the future more research is required to develop more applications for these ligands. Especially the hybrid imidate-phosphane ligand family showed already very impressive results in the asymmetric allylic alkylation and we expect that this will also be the case for other test reactions.

Part of this chapter has been published:

(1) Noël, T.; Vandyck, K.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J., "*Chiral Imidates: A New Class of Nitrogen-Based Chiral Ligands*", *Tetrahedron* **2009**, *65*, 8879-8884.

(2) Noël, T.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E; Van der Eycken, J., "*Efficient one-step synthesis of bidentate chiral oxazoline-alcohol ligands via a cyclic imidate ester rearrangement*", *Tetrahedron: Asymmetry* **2009**, *20*, 1962-1968.

(3) Noël, T.; Bert, K.; Van der Eycken, E.; Van der Eycken, J., "*Imidate-Phosphane Ligands as Highly Versatile Ligands for Palladium-Catalyzed Allylic Substitution Reactions*" (submitted for publication).

Part of this chapter has been patented:

(1) Noël, T.; Vandyck, K.; Van der Eycken, J. "*Cyclic Imidate Ligands*", UK Patent Application **0905995.7**

4.9 REFERENCES

[1] Caputo, C.A.; Jones, N.D. *Dalton Trans.* **2007**, 4627-4640.

[2] Fache, F.; Schulz, E.; Tommasino, M.L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159-2231.

[3] (a) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1989**, *28*, 60-61. (b) Nagata, T.; Yorozy, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem. Int. Ed.* **1995**, *34*, 2145-2147.

[4] Fache, F.; Dunjic, B.; Gamez, P.; Lemaire, M. *Top. Catal.* **1997**, *4*, 201-209.

[5] Togni, A.; Venanzi, L.M. *Angew. Chem. Int. Ed.* **1994**, *33*, 497-526.

[6] Crabtree, R.H. In *The Organometallic Chemistry of the Transition Metals*; Wiley, New Jersey, **1988**.

[7] Holyer, R.H.; Hubbard, C.D.; Kettle, S.F.A.; Wilkins, R.G. *Inorg. Chem.* **1965**, *4*, 929-935.

[8] Tolman, C.A. *Chem. Rev.* **1977**, *77*, 313-348.

[9] Seligson, A.L.; Trogler, W.C. *J. Am. Chem. Soc* **1991**, *113*, 2520-2527.

[10] Coe, B.J.; Glenwright, S.J. *Coord. Chem. Rev.* **2000**, *203*, 5-80.

[11] Patai, S. In *The Chemistry of Functional Groups: The Chemistry of Amidines and Imidates*; John Wiley & Sons: London, **1975**.

[12] Roger, R.; Neilson, D.G. *Chem. Rev.* **1961**, *61*, 179-211.

[13] Brotherton, T.K.; Lynn, J.W. *Chem. Rev.* **1959**, *59*, 841-883.

[14] Neilson, D.G. In *The Chemistry of Functional Groups: The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley & Sons: London, **1975**; pp 385-489.

[15] Häfelinger, G. In *The Chemistry of Functional Groups: The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley & Sons: London, **1975**; pp 1-84.

[16] Moriarty, R.; Yeh, C.-L.; Ramey, K.C.; Whitehurst, P.W. *J. Am. Chem. Soc.* **1970**, *92*, 6360-6362.

[17] Imidates as pharmacophores: (a) Bundgaard, H.; Larsen, J.D. *J. Med. Chem.* **1988**, *31*, 2066-2069. (b) Kini, G.D.; Robins, R.K.; Avery, T.L. *J. Med. Chem.* **1989**, *32*, 1447-1449.

[18] (a) Pinner, A.; Klein, F. *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1889-1897. (b) Pinner, A.; Klein, F. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 1475-1487. (c) Pinner, A. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 1643-1655.

[19] Kürti, L.; Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press, **2005**, pp 352-353.

[20] Schaefer, F.C.; Peters, G.A. *J. Org. Chem* **1961**, *26*, 412-418

[21] Kochi, T.; Ellman, J.A. *J. Am. Chem. Soc.* **2004**, *126*, 15652-15653.

[22] Restituyo, J.A.; Comstock, L.R.; Petersen, S.G.; Stringfellow, T.; Rajski, S.R. *Org. Lett.* **2003**, *5*, 4357-4360.

[23] (a) Yoo, E.J.; Bae, I.; Cho, S.H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347-1350. (b) Yoo, E.J.; Ahlquist, M.; Bae, I.; Sharpless, K.B.; Fokin, V.V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520-5528.

[24] (a) Saluste, C.G.; Crumpler, S.; Furber, M.; Whitby, R.J. *Tetrahedron Lett.* **2004**, *45*, 6995-6996. (b) Fernandez-Rivas, C.; Cardenas, D.J.; Martin-Matute, B.; Monge, A.; Gutierrez-Puebla, E.; Echavarren, A.M. *Organometallics* **2001**, *20*, 2998-3006.

[25] (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3935-3938. (b) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, *Tetrahedron* **2007**, *63*, 4793-4805.

[26] (a) Hargaden, G.; Guiry, P.J. *Chem. Rev.* **2009**, *109*, 2505-2550. (b) Rasappan, R.; Laventine, D.; Reiser, O. *Coord. Chem. Rev.* **2008**, *252*, 702-714. (c) Desimoni, G.; Faita, G.; Jørgensen, K.A. *Chem. Rev.* **2006**, *106*, 3561-3651. (d) Gómez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **2008**, *193-195*, 769-835. (e) Ghosh, A.K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45.

[27] Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339-345.

[28] Gupta, K.C.; Sutar, A.K. *Coord. Chem. Rev.* **2008**, *252*, 1420-1450.

[29] Canali, L.; Sherrington, D.C. *Chem. Soc. Rev.* **1999**, *28*, 85-93.

[30] (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem. Int. Ed.* **1990**, *29*, 205-207. (b) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169-1190. (c) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191-1203. (d) For a review about bipyridines: Fletcher, N.C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831-1842.

[31] Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227-4240.

[32] (a) Worch, C.: Mayer, A.C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis;* Toru, T.; Bolm, C., Eds.; Wiley/VCH, Weinheim, **2008**, pp 209-229. (b) Bolm, C. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D.; Jaeger, K.E., Eds.; Wiley/VCH, Weinheim, **2007**, pp 149-176. (c) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482-487. (d) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1-64.

[33] Vandyck, K.; Van der Eycken, J. *unpublished results.*

[34] (a) Stirling, C.J.M. *J. Chem. Soc.* **1960**, 255-262. (b) Okuyama, T.; Schmir, G.L. *J. Am. Chem. Soc.* **1972**, *94*, 8805-8811.

[35] Pirkle, W.H.; Sowin, T.J. *J. Org. Chem.* **1987**, *52*, 3011-3017.

[36] Yan, W.G.; Xu, B.L.; Guo, Z.R.; Liang, X.T.; Yang, G.Z. *Chin. Chem. Lett.* **2000**, *11*, 203-206.

[37] The odour of isonitriles or isocyanides is legendary as exemplified by a quote from Ugi: "*The development of the chemistry of isocyanides has probably suffered ... through the characteristic odour of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'. It is true that many potential workers in this field have been turned away by the odour."*

[38] (a) Verhoeven, T.R.; Reider, P.J. *Chem. Commun.* **1996**, *15*, 1753-1754. (b) Huang, Y.; Dalton, D.R.; Carroll, P.J. *J. Org. Chem.* **1997**, *62*, 372-376.

[39] Renson, M.; Collienne, R. *Bull. Soc. Chim. Belg.* **1964**, *73*, 491-506.

[40] (a) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 4389-4391. (b) Caiazzo, A.; Dalili, S.; Yudin, A.K. *Org. Lett.* **2002**, *4*, 2597-2600.

[41] Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345-350.

[42] (a) Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967. (b) Vandyck, K.; Matthys, B.; Willen, M.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Org. Lett.* **2006**, *8*, 363-366. (c) Yamamoto, K.; Momose, S.; Funahashi, M.; Ebata, S.; Ohmuro, H.; Komatsu, H.; Miyazawa, M. *Chem. Lett.* **1994**, *2*, 189-192.

[43] (a) Bedekar, A.V.; Koroleva, E.B.; Andersson, P.G. *J. Org. Chem.* **1997**, *62*, 2518-2526. (b) Trost, B.M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J.W. *Angew. Chem. Int. Ed.* **1995**, *34*, 2386-2388. (c) Kagan, H.B.; Dang, T.P. *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.

[44] Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581-1590.

[45] Vandyck, K. In *Synthese en toepassing van rigide C_2-symmetrische bidentaat liganden*, Ph.D. thesis, Universiteit Gent, **2006**.

[46] Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* **1987**, *87*, 779-794.

[47] Schweikart, K.-H.; Hanack, M.; Lüer, L.; Oelkrug, D. *Eur. J. Org. Chem.* **2001**, 293-302.

[48] (a) Littke, A.; Soumeillant, M.; Kaltenbach III, R.F.; Cherney, R.J.; Tarby, C.M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711-1714. (b) Jin, F.; Confalone, P.N. *Tetrahedron Lett.* **2000**, *41*, 3271-3273. (c) Maligres, P.E.; Waters, M.S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193-8195.

[49] (a) Percec, V.; Bae, J.-Y.; Hill, D.H. *J. Org. Chem.* **1995**, *60*, 6895-6903. (b) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776-2778. (c) Cassar, L. *J. Organomet. Chem.* **1973**, *54*, C57-C58.

[50] Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513-3526.

[51] Hodgson, H.H. *Chem. Rev.* **1947**, *40*, 251-277.

[52] (a) Li, C.-L.; Shieh, S.-J.; Lin, S.-C.; Liu, R.-S. *Org. Lett.* **2003**, *5*, 1131-1134. (b) Winn, M.; Reilly, E.B.; Liu, G.; Huth, J.R.; Jae, H.-S.; Freeman, J.; Pei, Z.; Xin, Z.; Lynch, J.; Kester, J.; von Geldern, T.W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G.F. *J. Med. Chem.* **2001**, *44*, 4393-4403.

[53] Sun, C.; Xu, B. *J. Org. Chem.* **2008**, *73*, 7361-7364.

[54] Doyle, M.P.; Siegfried, B.; Dellaria, J.F., Jr. *J. Org. Chem.* **1977**, *42*, 2426-2431.

[55] Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581-1590.

[56] Amoroso, D.; Graham, T.W.; Guo, R.; Tsang, C.-W.; Abdur-Rashid, K. *Aldrichimica Acta* **2008**, *41*, 15-26.

[57] Boaz, N.W.; Mackenzie, E.B.; Debenham, S.D.; Large, S.E.; Ponasik, J.A., Jr. *J. Org. Chem.* **2005**, *70*, 1872-1880.

[58] Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3-16.

[59] (a) Bauer, M.; Kazmaier, U.; *J. Organomet. Chem.* **2006**, *691*, 2155-2158. (b) Fu, B.; Du, D.-M.; Wang, J. *Tetrahedron: Asymmetry* **2004**, *15*, 119-126. (c) Jones, G.; Richards, C.J. *Tetrahedron: Asymmetry* **2004**, *15*, 653-664. (d) Braga, A.L.; Rubim, R.M.; Schrekker, H.S.; Wessjohann, L.A.; de Bolster, M.W.G.; Zeni, G.; Sehnem, J.A. *Tetrahedron: Asymmetry* **2003**, *14*, 3291-3295; (e) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2003**, *3*, 4259-4262; (f) Imai, Y.; Matsuo, S.; Zhang, W.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 239-241. (g) Zhang, W.; Yoshinaga, H.; Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 1512-1514. (h) Deng, W.-P.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 4689-4693.

[60] Bolm, C.; Muñiz, K.; Hildebrand, J.P. *Org. Lett.* **1999**, *1*, 491-493.

[61] Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860-7867.

[62] (a) Hall, J.; Lehn, J.M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1-6 (b) Allen, J.V.; Williams, J.M.J. *Tetrahedron: Asymmetry* **1994**, *5*, 277-282.

[63] Muniz Fernandez, K. In *Planar-chirale Liganden und Ligandensysteme: Stereoselektive Darstellung und Einsatz in der asymmetrischen Katalyse*, Ph.D. thesis, RWTH Aachen, **1998**.

[64] Kim, H.-J.; Kim, W.; Lough, A.J.; Kim, B.M.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16776-16777.

[65] (a) Pulkkinen, J.; Aburel, P.S.; Halland, N.; Jørgensen, K.A. *Adv. Synth. Catal.* **2004**, *346*, 1077-1080. (b) Halland, N.; Aburel, P.S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661-665. (c) Halland, N.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* **2002**, *67*, 8331-8338.

[66] (a) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5507-5510. (b) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K.A. *Chem. Commun.* **2005**, 4821-4823. (c) Oestreich, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2324-2327.

[67] Berkessel, A.; Gröger, H. In *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley, Weinheim, **2005**.

[68] Halland, N.; Hansen, T.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4955-4957.

[69] Jacobsen, E.N. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol.2, pp 607-618.

[70] Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905-2919.

[71] (a) Watson, I.D.G.; Yu, L.; Yudin, A.K. *Acc. Chem. Res.* **2006**, *39*, 194-206. (b) Padwa, A.; Murphree, S.S. *Arkivoc* **2006**, 6-33. (c) Osborn, H.M.I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693-1715.

[72] Evans, D.A.; Faul, M.M.; Bilodeau, M.T. *J. Org. Chem* **1991**, *56*, 6744-6746.

[73] Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; Anderson, B.A.; Barnes, D.M. *J.Am.Chem.Soc.* **1993**, *115*, 5328-5329.

[74] (a) Li, Z.; Quan, R.W.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1995**, *117*, 5889-5890. (b) Li, Z.; Conser, K.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1993**, *115*, 5326-5327.

[75] (a) Gillespie, K.M.; Sanders, C.J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C.P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450-3458. (b) Sanders, C.J.; Gillespie, K.M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132-7133.

[76] (a) Shi, M.; Wang, C.-J. *Chirality* **2002**, *14*, 412-416. (b) Shi, M.; Wang, C.-J.; Chan, A.S.C. *Tetrahedron: Asymmetry* **2001**, *12*, 3105-3111.

[77] Gillespie, K.M.; Crust, E.J.; Deeth, R.J.; Scott, P. *Chem. Commun.* **2001**, 785-786.

[78] Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol.2, pp 911-922.

[79] Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757-824.

[80] (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823-2824. (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841-842.

[81] (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071-6072. (b) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264-4268.

[82] (a) Fu, B.; Du, D.-M.; Wang, J. *Tetrahedron: Asymmetry* **2004**, *15*, 119-126. (b) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259-4262.

[83] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320-1367.

[84] (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233-6236. (b) Zhang, F.-Y.;Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585-589. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651-3655.

[85] (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327-6335. (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028-4036.

[86] For a review about dual stereocontrol: (a) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115-129. (b) Kim, Y.H. *Acc. Chem. Res.* **2001**, *34*, 955-962.

[87] (a) Szakonyi, Z.; Balázs, A.; Martinek, T.A.; Fülöp, F. *Tetrahedron: Asymmetry* **2006**, *17*, 199-204. (b) Zhong, Y.-W.; Jiang, C.-S.; Xu, M.-H.; Lin, G.-Q. *Tetrahedron* **2004**, *60*, 8861-8868. (c) Burguete, M.I.; Collado, M.; Escorihuela, J.; Galindo, F.; Garcia-Verdugo, E.; Luis, S.V.; Vicent, M.J. *Tetrahedron Lett.* **2003**, *44*, 6891-6894. (d) Altava, B.; Burguete, M.I.; Garcia-Verdugo, E.; Luis, S.V.; Miravet, J.F.; Vicent, M.J. *Tetrahedron: Asymmetry* **2000**, *11*, 4885-4893. (e) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805-9806.

[88] (a) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258-297. (b) Rovis, T. In *New Frontiers In Asymmetric Catalysis*; Mikami, K.; Lautens, M. Eds.; Wiley-VCH, **2007**; pp 276-278. (c) Trost, B.M.; Crawley, M.L. *Chem. Rev.* **2003**, *103*, 2921-2943. (d) Trost, B.M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH, **2000**; pp 593-650. (e) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin, 1999; Vol.2, pp 833-886. (f) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395-422.

[89] (a) Onodera, G.; Watabe, K.; Matsubara, M.; Oda, K.; Kezuka, S.; Takeuchi, R. *Adv. Synth. Catal.* **2008**, *350*, 2725-2732. (b) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 4595-4597. (c) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741-742.

[90] (a) Berkowitz, D.B.; Maiti, G. *Org. Lett.* **2004**, *6*, 2261-2264. (b) Berkowitz, D.B.; Shen, W.; Maiti, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2845-2851. (c) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc. Perkin Trans 1* **2000**, 15-18.

[91] Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Chem. Eur. J.* **2006**, *12*, 5178-5187.

[92] (a) Menard, F.; Chapman, T.M.; Dochendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569-4572. (b) Evans, P.A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158-7159. (c) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713-1715.

[93] Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37,* 159-167.

[94] Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435-4439.

[95] (a) Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Mahon, M.F.; Humphries, M.E.; Williams, J.M.J. *Chem. Eur. J.* **2000**, *6*, 353-360. (b) Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Williams, J.M.J. *Chem. Commun.* **1999**, 913-914.

[96] Trost, B.M.; Strege, P.E. *J. Am. Chem. Soc.* **1977**, *99*, 1649-1651.

[97] (a) Trost, B.M.; Krueger, A.C.; Bunt, R.C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520-6521. (b) Trost, B.M.; Bunt, R.C. *J. Am. Chem. Soc.* **1994**, *116*, 4089-4090. (c) Trost, B.M.; Van Vranken, D.L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327-9343. Trost, B.M.; Murphy, D.J. *Organometallics* **1985**, *4*, 1143-1145.

[98] Dierkes, P.; Ramdeehul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P.C.J.; van Leeuwen, P.W.N.M.; Osborn, J.A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3117-3118.

[99] (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336-345. (b) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523-1526. (c) von Matt, P.; Pfaltz, A. *Angew. Chem Int. Ed.* **1993**, *32*, 566-568.

[100] Popa, D.; Puigjaner, C.; Gómez, M.; Benet-Buchholz, J.; Vidal-Ferran, A.; Pericàs, M.A. *Adv. Synth. Catal.* **2007**, *349*, 2265-2278.

[101] Hu, X.; Chen, H.; Dai, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 3415-3421.

[102] Hu, X.; Dai, H.; Bai, C.; Chen, H.; Zheng, Z *Tetrahedron: Asymmetry* **2004**, *15*, 1065-1068.

[103] Evans, D.A.; Campos, K.R.; Tedrow, J.S.; Michael, F.E.; Gagné, M.R. *J. Org. Chem.* **1999**, *64*, 2994-2995.

[104] Pàmies, O.; Diéguez, M.; Claver, C. *Adv. Synth. Catal.* **2007**, *349*, 836-840.

[105] Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943-1947.

[106] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646-3647.

[107] (a) Schaffner, S.; Müller, J.F.K.; Neuburger, M.; Zehner, M. *Helv. Chim. Acta* **1998**, *81*, 1223-1232. (b) Liu, S.; Müller, J.F.K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283-293. (c) Schaffner, S.; Macko, L.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1997**, *80*, 463-471. (d) Baltzer, N.; Macko, L.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **1996**, *79*, 803-812.

[108] Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem. Int. Ed.* **1997**, *36*, 2108-2110.

[109] Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523-1526.

[110] For a ligand with a backbone analogous to imidate-phosphane ligands (**4.55**) an X-ray structure was found in the literature. In the solid state, the allylic moiety adopts an M-type conformation. However, attack of the nucleophile to this M-shaped intermediate would result in the formation of the *R*-product. This was not in agreement with the experimental results. It was shown that in solution the W-type conformation was the more reactive species and, hence, the observed formation of the *S*-enantiomer could be rationalized.: Tu, T.; Zhou, Y.G.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C.; Yu, Y.-H.; Sun, J. *Organometallics* **2003**, *22*, 1255-1265.

[111] (a) Blöchl, P.E.; Togni, A. *Organometallics* **1996**, *15*, 4125-4132. (b) Ward, T.R. *Organometallics* **1996**, *15*, 2836-2838.

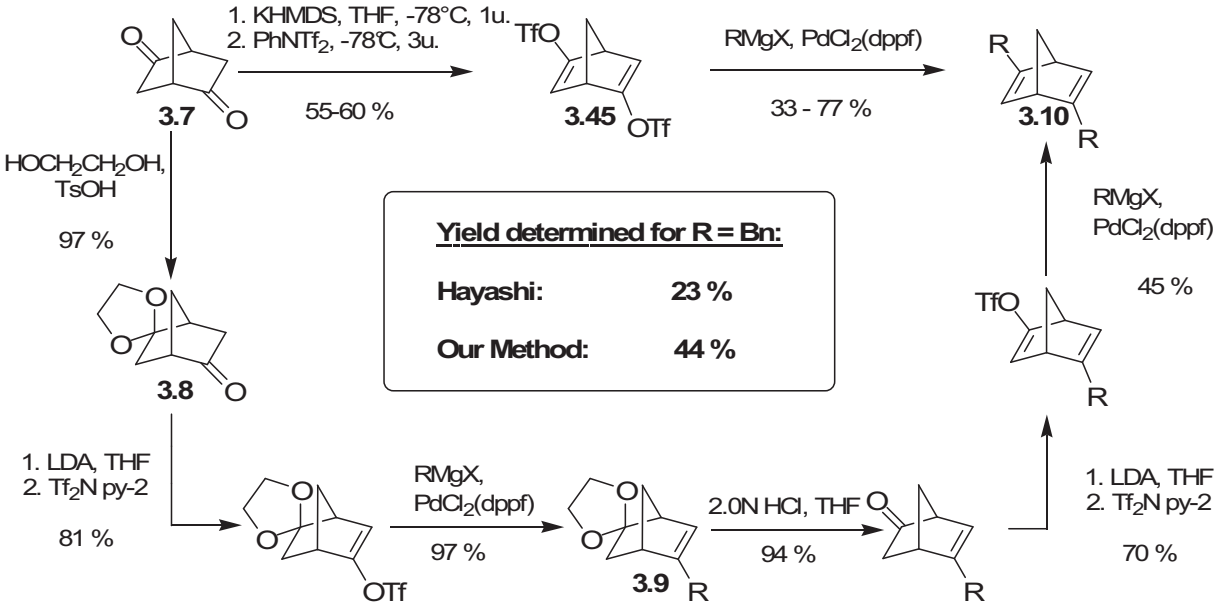
[112] Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P.S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031-1037.

5

SUMMARY AND FUTURE PERSPECTIVES

In this work, two main ligandclasses have been studied: chiral diene ligands and chiral imidate ligands. Both have in common that their use was, until recently, precluded from asymmetric catalysis due to their presumed instability.

In 2003, Hayashi *et al.* published the first paper about chiral diene ligands. Although the catalytic properties of these ligands were excellent, its synthesis was rather elaborate.[1] In chapter 3, we developed a novel route to synthesize chiral disubstituted bicyclo[2.2.1]heptadienes starting from enantiomerically pure bistriflate **3.45** (Scheme 5.1). Advantages of this approach are the higher overall yield and the possibility to introduce simultaneously both sidechains.[2]

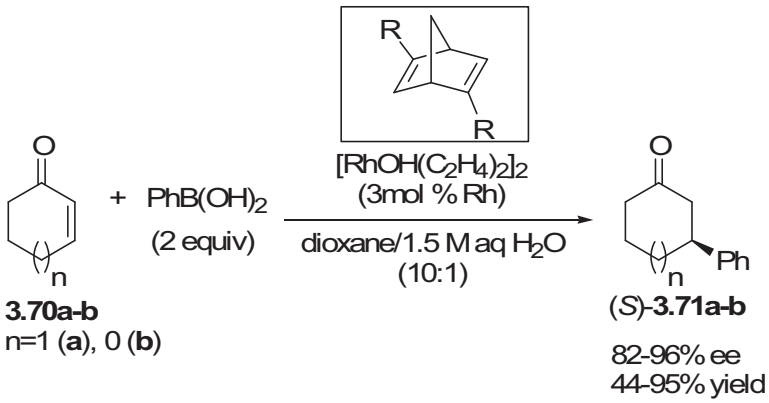


Scheme 5.1. *Comparison of our new method and the original method of Hayashi.*

With this method, we synthesized Hayashi's ligand with benzyl-sidechain and three new ligands (with R= *i*-Bu, *c*-Hex and Allyl). An NMR-study of the rhodium complex of

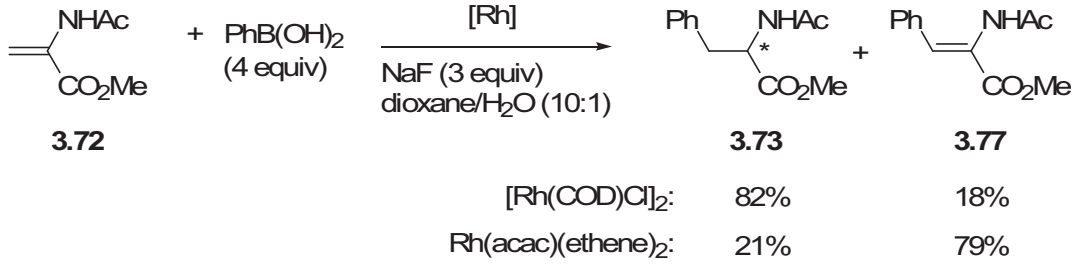
(*S*,*S*)-allyl-nbd* revealed that the coordination of the metal happened exclusively via the norbornadiene double bounds. This contrasts with the observations of Carreira.[3]

The synthesized diene ligands were tested in several rhodium-catalyzed asymmetric test reactions. Excellent enantioselectivities (up to 96% ee) were observed in the rhodium(I)-catalyzed 1,4-addition of phenylboronic acids to cyclic enones (scheme 5.2). An increasing sterical demand of the ligand substituents did not lead to a significant difference in selectivity, whereas the reaction rate was greatly influenced.



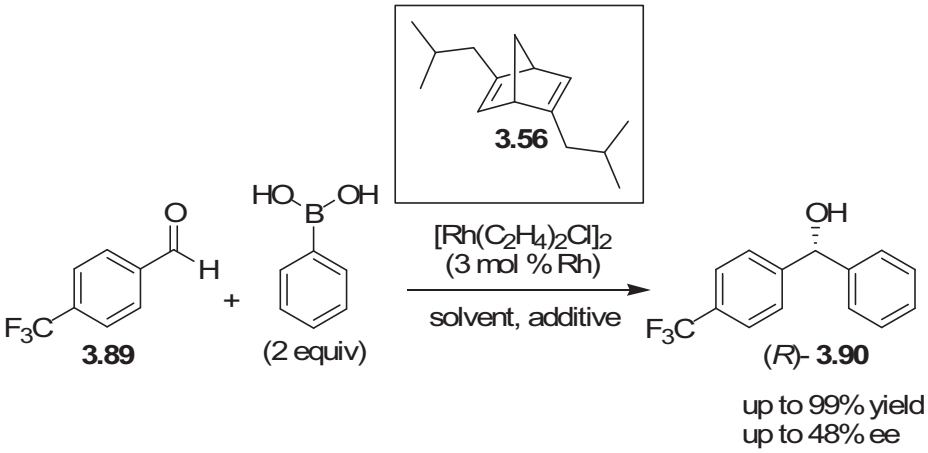
Scheme 5.2. *Rhodium(I)-catalyzed asymmetric 1,4-addition of $PhB(OH)_2$ to cyclic enones.*

In the 1,4-addition to α-acetamido acrylic ester **3.72**, the formation of a Heck-type product **3.77** was observed as a side product. Moreover, the ratio of the conjugate adduct (**3.73**) and Heck product (**3.77**) could be adjusted by the proper choice of the ligand in the achiral version (Scheme 5.3). When we turned to the asymmetric reaction with ligand **3.10**, low yields and selectivities were observed.



Scheme 5.3. *Rhodium(I)-catalyzed 1,4-addition versus Heck reaction.*

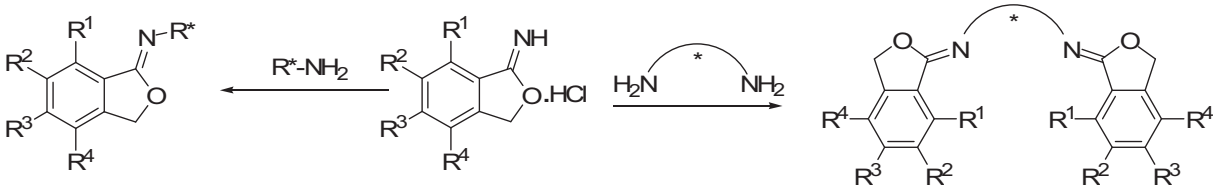
Finally, we investigated the rhodium-catalyzed 1,2-addition of phenylboronic acids to benzaldehydes. This reaction can be considered as a challenging reaction. The presence of the alkyl side chains on the ligand appeared to be crucial for the catalytic effect, resulting in a dramatically higher reactivity as compared to unsubstituted norbornadiene as a ligand. Enantioselectivities could be improved from poor to fair with ligand **3.56** (up to 48% ee) (Scheme 5.4).



Scheme 5.4. *Rhodium(I)-catalyzed asymmetric 1,2-addition of $PhB(OH)_2$ to p-trifluoromethylbenzaldehyde.*

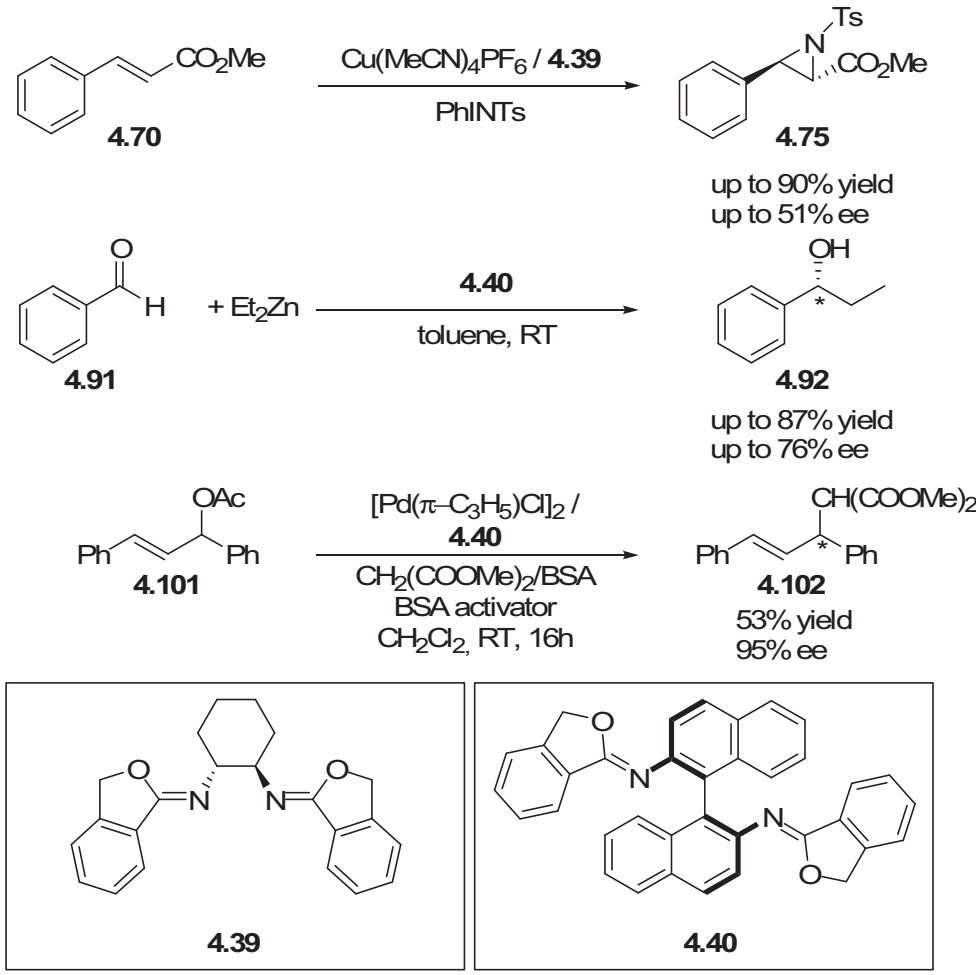
In chapter 4, we introduced chiral imidates as a novel nitrogen-based ligand family. Imidates have never before been reported in the literature. This is probably due to their general assumed instability.

The key factor which determines the utility of any ligand for asymmetric catalysis is the ease by which it can be accessed. We showed that these imidate ligands could be obtained readily via a one-step synthesis starting from a central precursor in excellent yields.[4] Moreover, imidate ligands could further be fine-tuned when substituents were put on the aromatic ring of the imidate ligand precursor (Scheme 5.5).



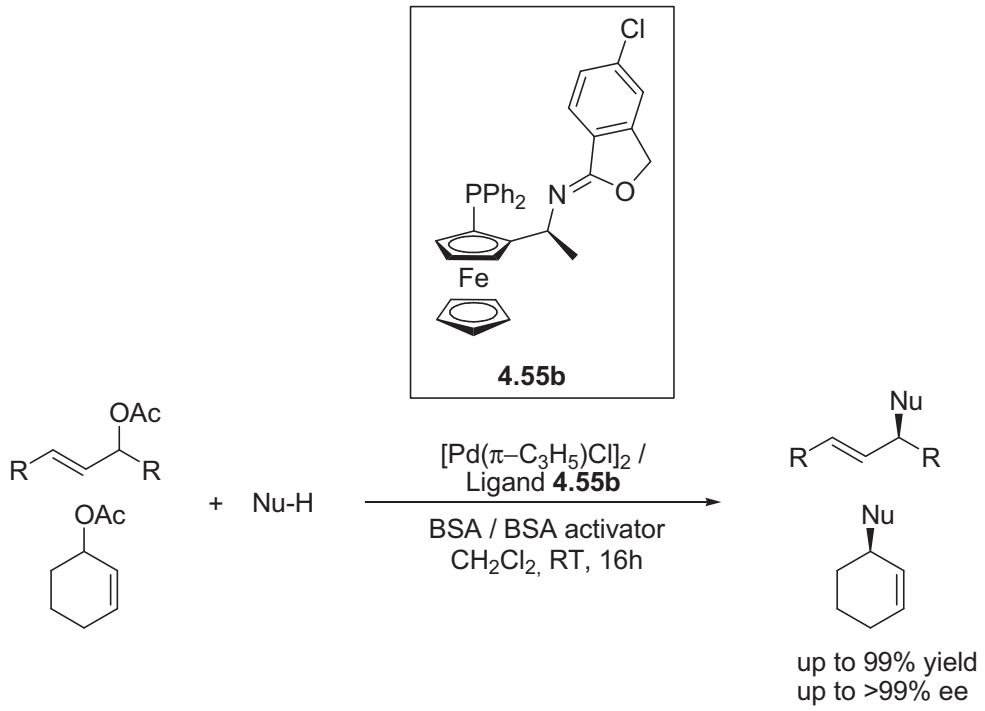
Scheme 5.5. *Synthesis of imidate ligand family.*

The synthesized monodentate and bidentate ligands were tested in several asymmetric test reactions (Scheme 5.6). In the copper(I)-catalyzed asymmetric aziridinations, we obtained usually high yields (up to 90% yield) and moderate enantioselectivity (51% ee) with ligand **4.39**. The asymmetric addition of diethylzinc to benzaldehyde resulted in high yields (up to 87% yield) and good enantioselectivities (up to 76% ee) with ligand **4.40**. However, the best result was obtained in the asymmetric allylic alkylation with ligand **4.40**: a moderate yield (53% yield) with an excellent selectivity (95% ee).

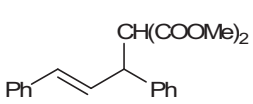
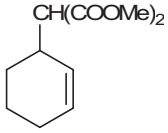
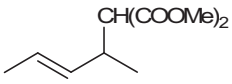
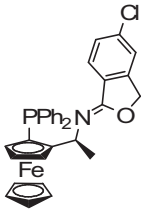
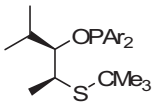
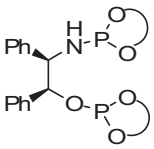
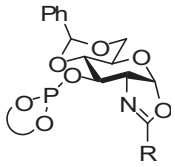
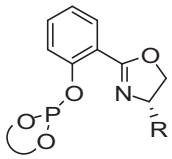


Scheme 5.6. *Application of bisimidate ligands in asymmetric aziridinations, asymmetric diethylzinc additions and asymmetric allylic alkylations.*

Futhermore, we developed successfully hybrid imidate-phosphane ligands as a new type of P,N ligands. These ligands are easily accessible in one step via a condensation of a commercially available aminophosphane and an imidate ligand precursor. The ligands were demonstrated to be highly valuable in palladium-catalyzed allylic substitution reactions (Scheme 5.7). Excellent performance of this catalyst system was observed in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with various nucleophiles (up to 99% yield and >99% ee). Moreover, the allylic alkylation of linear unhindered and cyclic substrates resulted in good conversions and enantioselectivities. Rarely are enantioselective catalysts successful in both substrate classes. Therefore, this imidate-phosphane ligand family can compete with a few other ligands which also provide high selectivities for both hindered and unhindered substrates (Table 5.1).



Scheme 5.7. *Pd-catalyzed asymmetric allylic alkylation with hybrid imidate-phosphane ligand* ***4.55b****.*

Entry	Ligand	 **4.98**	 **4.99**	 **4.100**	Reference
1	 **4.55b**	99% yield 99% ee	76% yield 74% ee	91% yield 83% ee	5
2		28% yield 91% ee	94% yield 91% ee	-	6
3[a]		100% conversion 96% ee	- 81% ee	- 82% ee	7
4[a]		100% conversion 92% ee	100% conversion 75% ee	- 81% ee	8
5[a]		100% conversion >99% ee	100% conversion 91% ee	100% conversion 73% ee	9

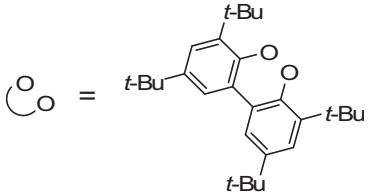
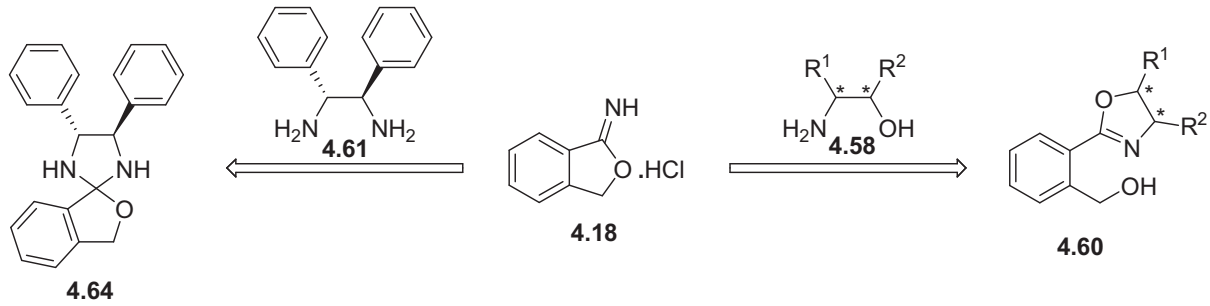
[a] 

Table 5.1. *Comparison of hybrid imidate-phosphane (**4.55b**) with the best in the literature existing results.*

The cyclic imidate ligand precursor **4.18** could also be used efficiently as a synthetic intermediate for the synthesis of chiral oxazoline alcohol ligands **4.60** and the synthesis of chiral imidazolidines **4.64** (Scheme 5.8). The chiral oxazoline alcohol ligands **4.60** were tested in asymmetric diethylzinc additions to benzaldehydes.[10] Enantioselectivities up to 87% ee were obtained.



Scheme 5.8. *Synthetic applications of cyclic imidate esters.*

In conclusion, we have shown that both chiral diene ligands as well as chiral imidate ligands can be very useful ligands for asymmetric catalysis.
We, as well as various other groups, showed that chiral dienes can be more than only a proof of concept. An impressive number of papers has been published to show their amazing catalytic properties.[11] However, it is remarkable that almost all examples concern rhodium- or iridium-catalyzed asymmetric reactions. Therefore, further research should be directed towards the search of new metals which are compatible with these diene ligands. This would expand the scope of the diene ligand family considerably.
Despite the fact that chiral imidate ligands are still at their infancy, we have demonstrated in this Ph.D.-thesis that they may be very interesting ligands in the future. Especially the easy and straightforward synthetic access to chiral imidates is of prime importance. This feature can help its widespread use in asymmetric transition metal catalysis. Future investigations should be directed towards the development of new applications for these imidate ligands. Especially the hybrid imidate-phosphane ligands have a lot of potential and should be further explored in other asymmetric test reactions.
Moreover, we showed briefly that it is possible to tune the catalytic properties of the imidate ligand by putting substituents on the aromatic ring of the imidate ligand precursor. This aspect should help to fine-tune the imidate catalyst system for a specific application.

REFERENCES

[1] Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.

[2] Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967.

[3] Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E.M. *Org. Lett.* **2004**, *6*, 3873-3876.

[4] Noël, T.; Vandyck, K.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Tetrahedron* **2009**, *65*, 8879-8884.

[5] Noël, T.; Bert, K.; Van der Eycken, E.; Van der Eycken, J. **2009** (submitted for publication).

[6] Evans, D.A.; Campos, K.R.; Tedrow, J.S.; Michael, F.E.; Gagné, M.R. *J. Org. Chem.* **1999**, *64*, 2994-2995.

[7] Pàmies, O.; Diéguez, M.; Claver, C. *Adv. Synth. Catal.* **2007**, *349*, 836-840.

[8] Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943-1947.

[9] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646-3647.

[10] Noël, T.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.; Van der Eycken, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1962-1968.

[11] For a review about chiral diene ligands: (a) Defieber, C.; Grützmacher, H.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4482-4502. (b) Johnson, J.B.; Rovis, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 840-871. (c) Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3364-3366.

6

EXPERIMENTAL SECTION

6.1 GENERAL

All reactions were carried out under argon atmosphere in dry solvents under anhydrous conditions, unless otherwise stated. Solvents were dried and distilled prior to use. Tetrahydrofuran, dioxane and diethylether were distilled from sodium/benzophenone. Dichloromethane, chloroform, 1,2-dichloroethane, pyridine, triethylamine were distilled from calciumhydride. DMF, DMSO, MeOH, chlorobenzene and acetonitrile were purchased as dry solvents. When needed, solvents were degassed prior to use by three freeze-pump-thaw cycles.

Analytical TLC was performed using Macherey-Nagel SIL G-25 UV_{254} plates. Visualization was performed via UV (254 nm) or via staining with potassium permanganate, cerium ammonium molybdate or ninhydrine. Flash chromatography was carried out with Rocc silicagel (0.040 – 0.063 mm).

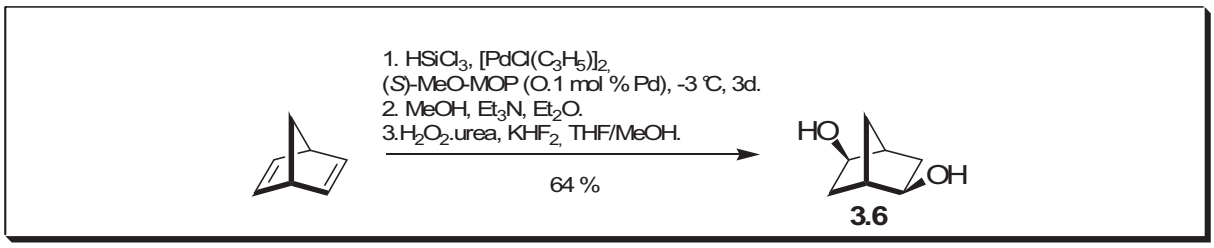
^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 300 or a Bruker AM 500 spectrometer as indicated, with chemical shifts reported in ppm relative to TMS, using the residual solvent signal as a standard. ^{13}C NMR spectra were recorded using the attached proton test. IR-spectra were recorded a Perkin-Elmer spectrum 1000 FT-IR spectrometer with a Pike Miracle HATR module.

EI Mass spectra were recorded with a Hewlett-Packard 5988A mass spectrometer. LC-MS analysis was performed on an Agilent 1100 series HPLC with quaternary pump, DAD and single quadrupole MS detector type VL with an API-ES source, using a Phenomenex Luna C18(2) column (250 x 4.6 mm, particle size 5 µm). Analytical chiral HPLC separations were performed on an Agilent 1100 series HPLC system with DAD detection. Exact molecular masses were measured on a Kratos MS50TC mass spectrometer. Melting points were measured with a Kofler melting point apparatus.

Norbornadiene was passed through neutral alumina and subsequently distilled. Cyclohexenone was distilled prior to use. $HSiCl_3$ was distilled from quinoline. Benzaldehyde was passed through basic alumina. All other reagents were purchased and used without purification, unless otherwise noted.

6.2 SYNTHESIS OF CHIRAL DIENE LIGANDS

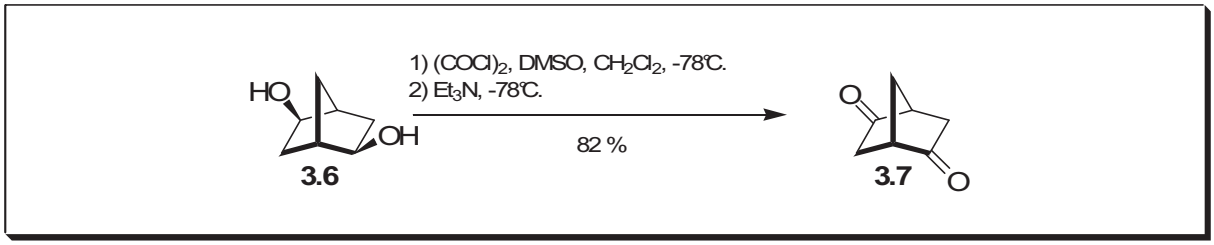
6.2.1 Synthesis of (1*S*, 2*R*, 4*S*, 5*R*)-2,5-dihydroxybicyclo[2.2.1]heptane (3.6)



A solution of $[PdCl(\pi\text{-}C_3H_5)]_2$ (13.7 mg, 37.4 µmol) and (*S*)-MeO-MOP (70 mg, 149 µmol) in benzene (2 mL) and pyridine (0.1 mL) was placed in a double-jacketed 50 mL flask, provided with a thermometer, under argon. $HSiCl_3$ (18 mL, 179 mmol) was added and the solution was cooled to -3 °C. Norborn adiene (8.06 mL, 75 mmol) was added slowly with a syringe pump (2 mL/h). The temperature in the reaction vessel was kept constant at -3 °C. The reaction was stirre d for ca. 3 days, until it turned into a pale yellowish solid. The solvent and excess $HSiCl_3$ were removed in *vacuo* at room temperature. The residue was dissolved in 50.0 mL of dry Et_2O under argon and cooled to 0 °C. A mixture of dry MeOH (545.0 mL , 1.34 mol), dry Et_3N (72.0 mL, 0.552 mol) and dry Et_2O (50.0 mL) was added dropwise. After the solution was stirred at room temperature overnight, the precipitated salts were filtered off and washed with Et_2O. The filtrate was concentrated in vacuo to yield a brownish oil. To this was added KHF_2 (29.17 g, 374 mmol), dry THF (80 mL), dry MeOH (80 mL) and H_2O_2.urea (52.70 g, 560 mmol). The resulting white suspension was stirred overnight at 60 °C. The solids were filtered off and washed with MeOH. The filtrate was concentrated in vacuo to yield a white solid. This was dissolved in 150 mL sat. aq. NH_4Cl and extracted with 6 x 500 mL $CHCl_3$/EtOH (70/30). The combined organic phases were dried over Na_2SO_4 and evaporated. Diol **1** (>99% ee) was isolated as a white solid after flash chromatography over silicagel (EtOAc/pentane, 75/25), 6.08 g (64 % based on norbornadiene).

Formula: $C_7H_{12}O_2$ (128.17 g/mol).
R_f (EtOAc/Et_2O 75:25): 0.24
^{1}H-NMR (500 MHz, pyridine-d_5): δ 1.58-1.59 (m, 4H), 2.02 (s, 2H), 2.42 (s, 2H), 3.94 (t, J= 4.5 Hz, 2H), 5.94 (br s, 2H) ppm.
^{13}C-NMR (75.4 MHz, pyridine-d_5): δ 31,2 (CH_2), 37.7 (CH_2), 44.2 (CH), 73.5 (CH) ppm.
IR (KBr, thin film): 3233, 2960, 2931, 2889, 1351, 1088, 993, 744 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 110 (M^+-H_2O, 17), 92 (8), 81 (21), 66 (100), 55 (38), 41 (45).
Melting Point (°C) : 162 °C.
Optical rotation: $[\alpha]_D^{20} = +8.8$ (*c* 1.0, EtOH).

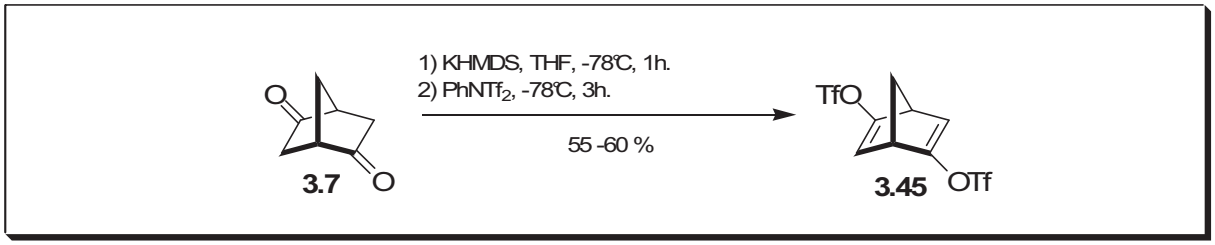
6.2.2 Synthesis of (1*S*,4*S*)-Bicyclo[2.2.1]heptane-2,5-dione (3.7)



Dry CH_2Cl_2 (500.0 mL) was cooled to -78 °C and oxalylchloride (18.0 mL, 189 mmol) was added under argon and magnetic stirring. DMSO (26.8 mL, 378 mmol) was added dropwise and the solution was stirred for 5 min. Diol **3.6** (6.10 g, 43 mmol) was dissolved in 1000 mL dry CH_2Cl_2 and canulated to the Swern reagent. The resulting solution was stirred for another 20 min. Et_3N (104.0 mL, 686 mmol) was added, and after 1 h TLC indicated complete conversion of the diol. 1 N HCl (500 mL) was added and the mixture was extracted with CH_2Cl_2/Et_2O (1/1; 4x500 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (1000 mL) and brine (1000 mL) and dried over $MgSO_4$. The filtrate was concentrated in vacuo. The resulting yellow oil was purified by flash chromatography over silicagel (Et_2O/pentane, 2/1) resulting in a white solid, giving 4.82 g (82 %) of diketone **3.7** (>99% ee).

Formula: $C_7H_8O_2$ (124.14 g/mol).
R_f (Et_2O/pentane 2:1): 0.23
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.08-2.10 (m, 2H), 2.10-2.18 (ddd, *J*= 2, 4, 18 Hz, 2H), 2.33-2.42 (ddd, *J*= 2, 4, 18 Hz, 2H) 2.97-3.00 (td, *J*= 1.6, 6.2 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 36.4 (CH_2), 39.0 (CH_2), 48.6 (CH), 212.3 (C) ppm.
IR (KBr, thin film): 2960, 1753, 1736, 1406, 1268, 1232, 1188, 1124, 1000, 963 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 124 (M^+, 100), 95 (18), 82 (26), 67 (99), 55 (86), 50 (8), 41 (34).
Melting Point (°C) : 118-128 °C.
Optical rotation: $[\alpha]_D^{20} = -3.1$ (*c* 1.0, $CHCl_3$).
Chiral HPLC: Chiralcel OJ-H kolom, solvent: *n*-hexane/EtOH (90:10), flow rate= 1 mL/min, T= 35°C, retention times: 14.9 min for (1*R*, 4*R*)-**3.7**, 16.2 min for (1*S*, 4*S*)-**3.7**.

6.2.3 Synthesis of bis-triflate (*S*,*S*)-3.45

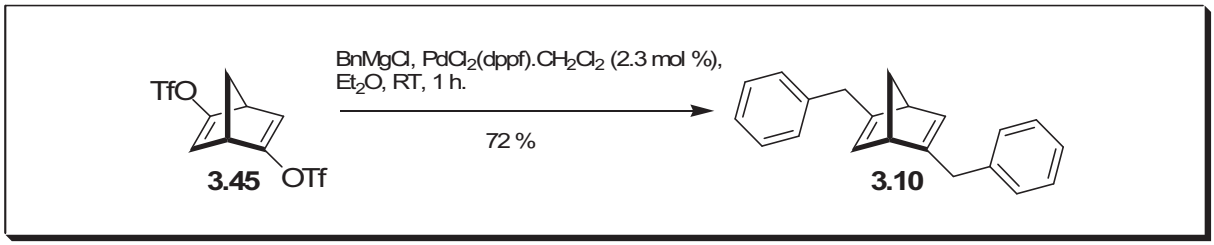


Diketone (1*S*,4*S*)-**3.7** (4.0 g, 31.8 mmol) was dissolved in dry THF (220 mL) and cooled to -78 °C. KHMDS (166 mL, 0.5 M in toluene, 82.8 mmol) was added dropwise. After 1 h $PhNTf_2$ (29.6 mL, 82.8 mmol) dissolved in 120 mL dry THF was added. The resulting reaction mixture was stirred for another 3 h. The reaction mixture was quenched with saturated aq. NH_4Cl (300 mL) and extracted with pentane (2 x 500 mL). The combined organic phases were washed with saturated aq. NH_4Cl (200 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting brown oil was purified by flash chromatography over silicagel (gradient elution with pentane/$CHCl_3$, 96/4 to pentane/Et_2O, 95/5) resulting in a colourless oil, giving 7.08 g (55 %) of bis-triflate **3.45**.

Formula: $C_9H_6F_6O_6S_2$ (388.25 g/mol).
R_f (pentane/Et_2O 95:5): 0.44
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.62 (t, *J*= 1.8 Hz, 2H), 3.53 (m, 2H), 6.51 (dd (app.t), *J*= 2.4, 2.4 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$ $CDCl_3$): δ 50.3 (CH), 73.1 (CH_2), 118.4 (q, $J_{C\text{-}F}$ = 321 Hz, C), 123.7 (CH), 168.2 (C) ppm.
IR (KBr, thin film): 1632, 1609, 1426, 1294, 1247, 1207, 1135, 1073, 1023, 934, 882, 845 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 388 (M^+, 9), 227 (4), 149 (6), 122 (9), 105 (10), 77 (41), 69 (100), 41 (26).
Optical rotation: $[\alpha]_D^{20} = -28$ (*c* 1.0, $CHCl_3$)

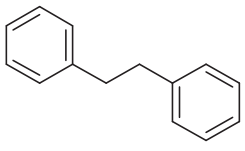
6.2.4 A typical procedure for the preparation of (*S,S*)-nbd*-ligands

6.2.4.1 Synthesis of (*S,S*)-Bn-nbd* (3.10)



A solution of bis-triflate (*S,S*)-**3.45** (104.7 mg, 269.7 µmol) and $PdCl_2(dppf).CH_2Cl_2$ (4.7 mg, 5.79 µmol) in Et_2O (1.0 mL) was cooled in an ice bath . To the resulting red suspension was added BnMgCl (1.35 mL, 1.77 mmol, 20 w/w% in THF) under argon. The reaction mixture was stirred for 1 h at room temperature, quenched with brine (25 mL) and extracted with EtOAc (4x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (isooctane/$CHCl_3$, 96/4) resulting in a white solid which contained a significant amount of diphenylethane which was removed under reduced pressure (< 1 mm Hg, 1 night) resulting in pure (*S,S*)-Bn-nbd* (**3.10**) as a white solid, 53.0 mg (72 %).

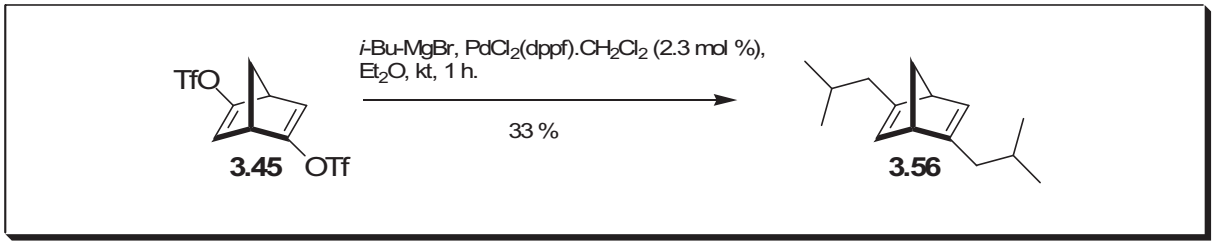
Formula: $C_{21}H_{20}$ (272.38 g/mol).
R_f (isooctane/$CHCl_3$ 96:4): 0.21
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.94 (t, *J*= 1.7 Hz, 2H), 3.14 (dt, *J*= 3.8, 1.7 Hz, 2H), 3.49 (s, 4H), 6.02 (dt, *J*= 3.8, 1.6 Hz, 2H), 7.09 (d, *J*= 7.2 Hz, 4H), 7.18 (tt, *J*= 7.2, 1.2 Hz, 2H), 7.26 (t, *J*= 7.2 Hz, 4H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 38.0 (CH_2), 53.1 (CH), 71.4 (CH_2), 125.9 (CH), 128.1 (CH), 129.0 (CH), 134.3 (CH), 139.1 (C), 156.9 (C) ppm.
IR (KBr, thin film): 2970, 2950, 2929, 2878, 1600, 1492, 1451, 1306, 1183, 1069, 1026, 948, 856, 780, 752, 737, 708 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 272 (M^+, 9), 181 (34), 165 (21), 156 (34), 141 (17), 128 (22), 115 (39), 103 (8), 91 (88), 84 (29), 65 (30), 49 (71), 40 (100).
APCI-MS: 273 $[M+H]^+$.
Melting Point (℃) : 67 ℃.
Optical rotation: $[\alpha]_D^{20} =$ - 180 (*c* 1.07, $CHCl_3$).
HRMS (EI): calcd for $C_{21}H_{20}$: 272.1565; found 272.1569.



Formula: $C_{14}H_{14}$ (182.26 g/mol).
R_f (isooctane/$CHCl_3$ 96:4): 0.27
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.95 (s, 4H), 7.23 (m, 6H), 7.31 (m, 4H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 37.98 (CH_2), 125.94 (CH), 128.36 (CH), 128.48 (CH), 141.81 (C) ppm.

IR (KBr, thin film): 3058, 3026, 2944, 1600, 1491, 1450, 1063, 1027, 750, 698, 517 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 182 (M^+, 21), 91 (100), 77 (3), 65 (20), 51 (7), 41 (2).
Melting Point (℃) : 51-52 ℃.

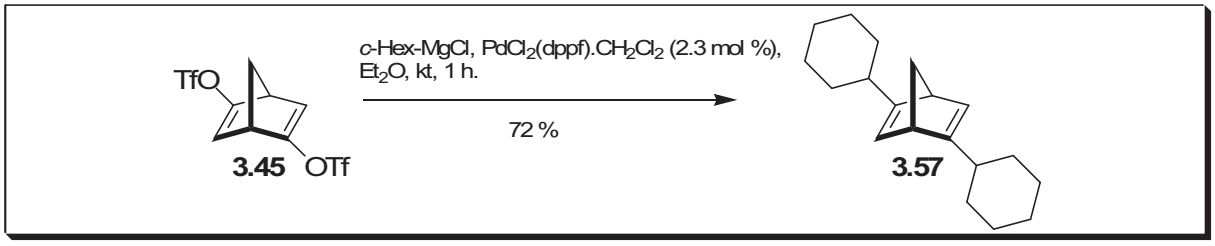
6.2.4.2 Synthesis of (*S,S*)-*i*-Bu-nbd* (3.56)



The reaction was performed on bis-triflate (*S,S*)-**3.45** (501.3 mg, 1.29 mmol) using a *i*-BuMgCl (4.5 mL, 8.99 mmol, 2 M in Et_2O) solution. After 1 h the reaction was quenched with H_2O and extracted with pentane. The combined organic phases were dried on $MgSO_4$ and carefully concentrated in vacuo. Purification by flash chromatography over silicagel (pentane) resulted in pure (*S,S*)-*i*-Bu-nbd* (**3.56**) as a colourless oil, 86.7 mg (33 %).

Formula: $C_{15}H_{24}$ (204.35 g/mol).
R_f (isooctane): 0.56
^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.81 (d, *J*= 6.6 Hz, 6H), 0.87 (d, *J*= 6.6, 6H), 1.71-1.80 (septet, *J*= 6.6 Hz, 2H), 1.94 (t, *J*= 1.6 Hz, 2H), 2.03-2.08 (dq, *J*= 1.5, 6.8 Hz, 4H), 3.17 (dt, *J*= 3.9, 1.6 Hz, 2H), 6.12 (td, *J*= 1.5, 3.9 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 22.6 (CH_3), 22.8 (CH_3), 26.6 (CH), 41.0 (CH_2), 53.4 (CH), 71.9 (CH_2), 133.5 (CH), 157.9 (C) ppm.
IR (KBr, thin film): 3062, 2955, 2930, 2900, 2867, 2830, 1464, 1383, 1366, 1298, 1185, 1167, 780 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 204 (M^+, 49), 161 (27), 147 (25), 122 (48), 117 (20), 105 (60), 91 (51), 80 (100), 66 (44), 43 (77).
APCI-MS: 205 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20} =$ - 103 (*c* 1.14, $CHCl_3$).
HRMS (EI): calcd for $C_{15}H_{24}$: 204.1878; found 204.1873.

6.2.4.3 Synthesis of (*S,S*)-*c*-Hex-nbd* (3.57).

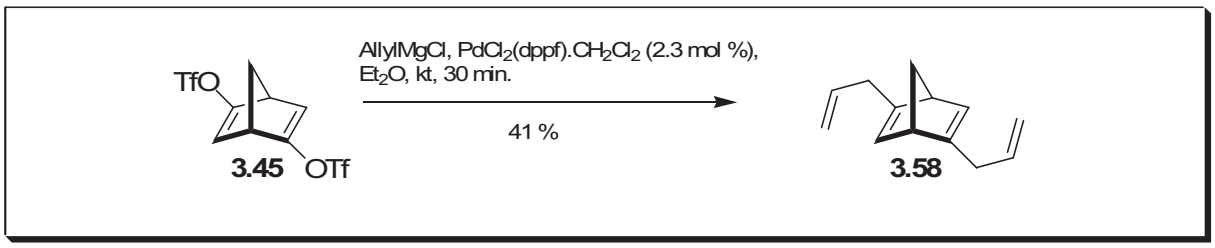


The reaction was performed on bis-triflate (*S,S*)-**3.45** (101.0 mg, 257.6 µmol) using a *c*-HexMgCl (0.9 mL, 177 µmol, 2 M in Et_2O) solution. After 1 h the reaction was

quenched with H_2O and extracted with pentane. The combined organic phase were dried on $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography over silicagel (pentane) resulted in pure (*S,S*)-*c*-Hex-nbd* (**3.57**) as a colourless oil, 51.0 mg (77 %).

Formula: $C_{19}H_{28}$ (256.43 g/mol).
R_f (isooctane): 0.55
^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.95-1.04 (m, 2H), 1.05-1.20 (m, 4H), 1.22-1.32 (m, 4H), 1.62-1.79 (m, 10H), 1.84 (t, *J*= 1.6 Hz, 2H), 2.08 (m, 2H), 3.26 (dt, *J*= 3.9, 1.6 Hz, 2H), 6.02 (td, *J*= 1.6, 3.9 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 26.2 (CH_2), 26.5 (CH_2), 31.1 (CH_2), 31.2 (CH_2), 39.8 (CH), 51.7 (CH), 71.1 (CH_2), 130.7 (CH), 164.1 (C) ppm.
IR (KBr, thin film): 3059, 2960, 2923, 2850, 1448, 1276, 1184, 890, 806, 788 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 256 (M^+, 43), 189 (15), 173 (33), 148 (51), 131 (21), 117 (24), 105 (34), 91 (58), 79 (38), 55 (69), 41 (100).
APCI-MS: 257 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 58 (*c* 0.96, $CHCl_3$).
HRMS (EI): calcd for $C_{19}H_{28}$: 256.2191; found 256.2190.

6.2.4.4 Synthesis of (*S,S*)-Allyl-nbd* (3.58).

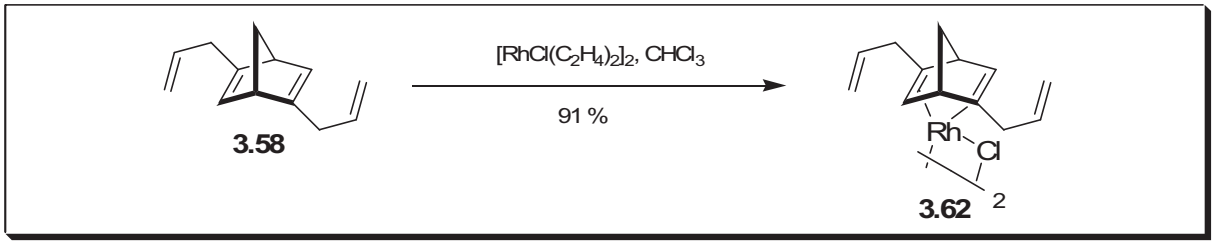


The reaction was performed on bis-triflate (*S,S*)-**3.45** (508.5 mg; 1.31 mmol) using an allylMgBr solution (8.85 mL, 8.99 mmol, 1 M in Et_2O) . After 30 min the reaction was quenched with H_2O and extracted with pentane. The combined organic phases were dried over $MgSO_4$ and carefully concentrated in vacuo. Purification by flash chromatography over silicagel (pentane) resulted in pure (*S,S*)-allyl-nbd* (**3.58**) as a colourless oil, 92.5 mg (41 %).

Formula: $C_{13}H_{16}$ (172.27 g/mol).
R_f (isooctane): 0.55
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.97 (t, *J*= 1.6 Hz, 2H), 2.93 (m, 4H), 3.22 (dt, *J*= 4.0, 1.6 Hz, 2H), 5.01 (ddt, *J*= 10.0, 1.2, 1.2 Hz, 2H), 5.04 (ddd, *J*= 17.0, 1.6, 3.4 Hz, 2H), 5.79 (tdd, *J*= 3.5, 10.0, 17.0 Hz, 2H), 6.18 (td, *J*= 1.7, 4.0 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 36.0 (CH_2), 53.3 (CH), 71.8 (CH_2), 115.7 (CH_2), 133.5 (CH), 135.7 (CH), 157.0 (C) ppm.
IR (KBr, thin film): 3076, 2972, 2932, 2866, 1640, 1607, 1427, 1301, 1263, 1185, 993, 912, 786 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 172 (M^+, 5), 131 (45), 115 (28), 106 (18), 91 (100), 78 (62), 65 (18), 51 (18), 41 (18).
APCI-MS: 173 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 151.1 (*c* 1.06, $CHCl_3$).

HRMS (EI): calcd for $C_{13}H_{16}$: 172.1252; found 172.1259.

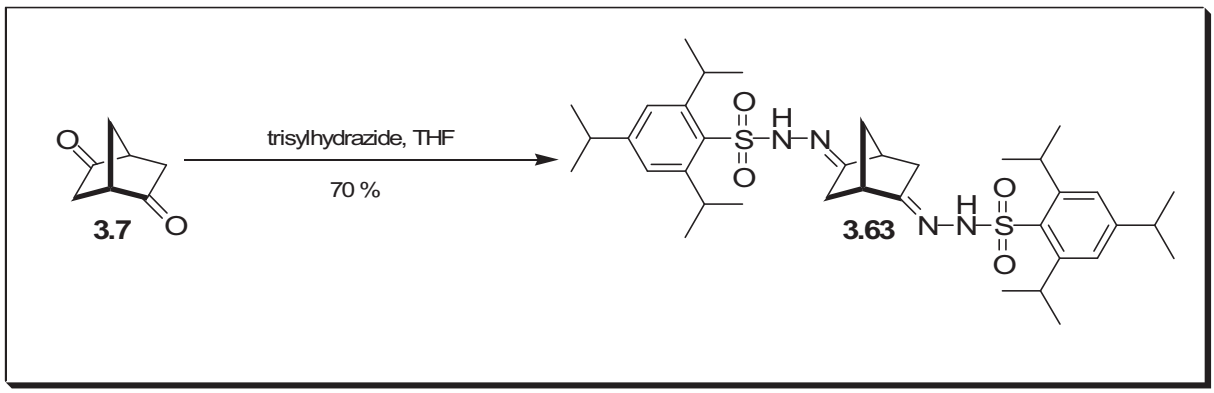
6.2.5 Synthesis of [RhCl ((*S,S*)-allyl-nbd*)]$_2$ (3.62)



(*S,S*)-Allyl-nbd* (**3.58**) (16.9 mg, 98.1 µmol) and [RhCl(C_2H_4)$_2$]$_2$ (17.9 mg, 92.0 µmol Rh) were dissolved in $CHCl_3$ (5 mL) and stirred for 3 h under argon. Purification by flash chromatography over silicagel (hexane/CH_2Cl_2, 60:40) resulted in pure [RhCl((*S,S*)-allyl-nbd*)]$_2$ (**3.62**) as a yellowish oil, 25.9 mg (91 %).

Formula: $C_{26}H_{32}Cl_2Rh_2$ (621.25 g/mol).
R_f (hexane/CH_2Cl_2 60:40): 0.48
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 4H), 2.45 (dd, *J*= 6.9, 14.6 Hz, 4H), 2.94 (dd, *J*= 7.0, 14.6 Hz, 4H), 3.57 (m, 4H), 3.60 (m, 4H), 5.17 (dd, *J*= 1.0, 10.0 Hz, 4H), 5.27 (dd, *J*= 1.2, 17.0 Hz, 4H), 6.37 (tdd, *J*= 3.2, 10.0, 17.0 Hz, 4H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 38.5 (CH_2), 47.4 (d, $J_{C\text{-}Rh}$= 10.6 Hz, CH), 53.1 (d, $J_{C\text{-}Rh}$= 3.0 Hz, CH), 59.5 (d, $J_{C\text{-}Rh}$= 7.5 Hz, CH_2), 69.4 (d, $J_{C\text{-}Rh}$= 11.3 Hz, C), 116.6 (CH_2), 135.4 (CH) ppm.
IR (KBr, thin film): 3071, 2988, 2911, 1634, 1422, 1307, 1234, 1170, 991, 913 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 620 (M^+, 44), 584 (9), 548 (26), 412 (100), 372 (41), 346 (12), 308 (9), 273 (56), 218 (41), 205 (33), 168 (15), 115 (20), 103 (24), 77 (20), 49 (22).
ES-MS: 584.9 ([RhOH((*S*,*S*)-allyl-nbd*)]$_2$ + H^+), 275 (Rh^+(*S*,*S*)-allyl-nbd*).
Optical rotation: $[\alpha]_D^{20}$ = + 3.4 (*c* 0.90, $CHCl_3$).
HRMS (EI): calcd for $C_{26}H_{32}Cl_2Rh_2$: 619.9991; found 620.0003.

6.2.6 Synthesis of trisylhydrazon (3.63)



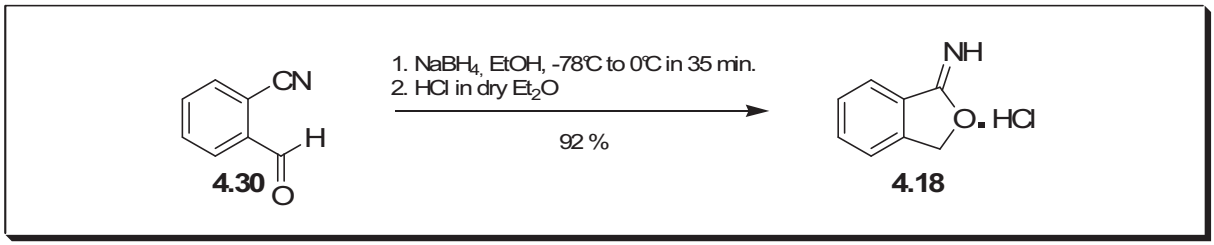
Diketone **3.72** (100 mg, 0.806 mmol) and trisylhydrazide (481 mg, 1.612 mmol) are dissolved in 5 mL dry THF and stirred for 24 h at room temperature. Evaporation of

the reaction mixture and purification via flash chromatography over silicagel (hexane/EtOAc, 80:20 + 1% Et_3N) resulted in pure trisylhydrazon (**3.63**) as a white powder, 384.0 mg (70 %).

Formula: $C_{37}H_{56}N_4O_4S_2$ (684.99 g/mol).
R_f (hex/EtOAc 80:20): 0.24
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.29-1.33 (d, *J*= 6.8 Hz, 18H), 1.33-1.36 (d, *J*= 6.8 Hz, 18H), 1.77 (s, 2H), 2.07-2.13 (d, *J*= 16.7 Hz, 2H), 2.30-2.40 (dd, *J*= 3.0, 16.7 Hz, 2H), 3.0 (septet, *J*= 6.8 Hz, 2H), 3.2 (d, *J* = 3.0 Hz, 2H), 4.26 (septet, *J*= 6.8 Hz, 4H), 7.13 (br s, 2H), 7.26 (s, 2H), 7.36 (s, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 23.6 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 29.9 (CH), 32.6 (CH_2), 34.2 (CH), 39.1 (CH_2), 43.9 (CH), 123.9 (CH), 131.1 (C), 151.3 (C), 153.4 (C), 161.8 (C) ppm.
IR (KBr, thin film): 3204, 2959, 2869, 1599, 1563, 1462, 1426, 1383, 1363, 1326, 1164, 1153, 1103, 1030, 995, 940, 904, 722, 660, 563 cm^{-1}.
APCI-MS: 685.3 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 68.7 (*c* 1.0, $CHCl_3$).
Melting Point (℃) : decomposition.

6.3 SYNTHESIS OF CHIRAL IMIDATE LIGANDS

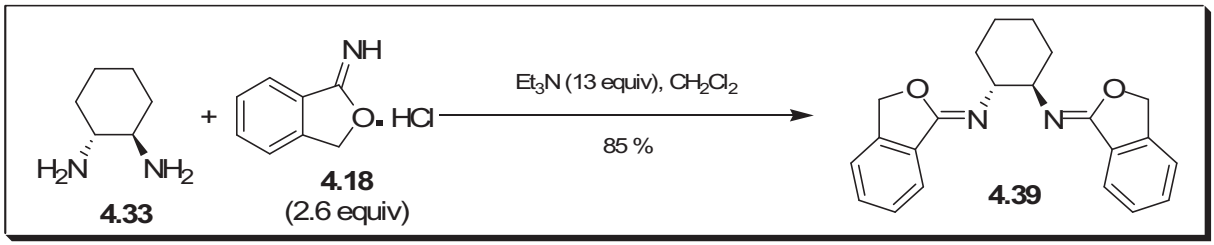
6.3.1 Synthesis of 1,3-dihydro-iminobenzofuran hydrochloride (4.18)



2-Cyanobenzaldehyde **4.30** (7.0 g, 53.4 mmol) was dissolved in absolute ethanol (420 mL) and cooled to -78°C. $NaBH_4$ (2.02 g, 53.4 mmol) was added and the reaction mixture was allowed to warm to 0°C in 30 min. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3 x 1000 mL). The organic phases were dried over Na_2SO_4 and concentrated in vacuo. The resulting orange oil was dissolved in dry CH_2Cl_2 (165 mL) and dry HCl in Et_2O (65 mL) was added. The resulting suspension was filtrated and the white crystals were washed with dry THF. This resulted in 8.3 g (92 %) of imidate hydrochloride **4.18**.

Formula: C_8H_8ClNO (169.61 g/mol).
R_f (CH_2Cl_2/MeOH, 90/10): 0.53
^{1}H-NMR (300 MHz, CD_3OD): δ 5.99 (s, 2H), 7.76 (t, *J*= 7.8 Hz, 1H), 7.84 (d, *J*= 7.8 Hz, 1H), 7.98 (t, *J*= 7.8 Hz, 1H), 8.33 (d, *J*= 7.8 Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, CD_3OD): 81.0 (CH_2), 123.9 (CH), 124.6 (C), 126.5 (CH), 131.1 (CH), 138.1 (CH), 148.9 (C), 178.4 (C) ppm.
IR (HATR): 3422, 3357, 3062, 3036, 2924, 2806, 2717, 2628, 1676, 1617, 1592, 1560, 1486, 1446, 1330, 1318, 1222, 1080, 938, 794, 739 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 133 ((M^+-HCl), 50), 104 (100), 89 (15), 77 (44), 63 (14), 51 (20), 43 (7). ES-MS: 134 $[M\text{-}Cl^-]^+$.
Melting Point (°C) : decomposition.
HRMS (EI): calcd for C_8H_7NO: 133.0528; found 133.0533.

6.3.2 Synthesis of (1*R*, 2*R*)-N,N'-bis-(3*H*-isobenzofuran-1-ylidene)-cyclohexane-1, 2-diamine (4.39).

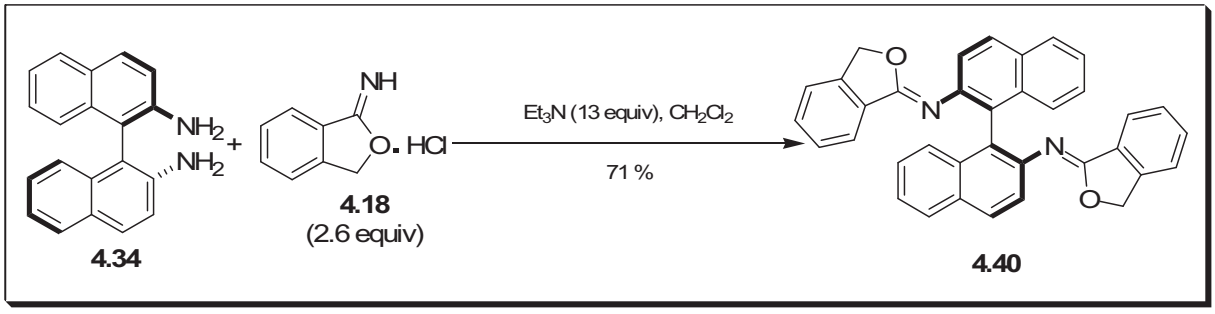


A suspension of (1*R*, 2*R*)-(-)-diaminocyclohexane (**4.33**) (119 mg, 1.04 mmol) and imidate **4.18** (450 mg, 2.65 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (1 mL, 13.6 mmol) was added and the resulting suspension was refluxed for 24h. The reaction mixture was passed through a short pad of silicagel and eluted with

EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/Et_2O, 6/4, + 1% Et_3N) resulted in **4.39** as a white solid, 308 mg (85 %).

Formula: $C_{22}H_{22}N_2O_2$ (346.42 g/mol).
R_f (toluene/Et_2O, 6/4, + 1% Et_3N): 0.23
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.47 (m, 2H) 1.60 (m, *J*= 1.9, 10.7 Hz, 2 H), 1.80 (m, *J*= 1.9 Hz, 2H), 1.92 (m, *J*= 3.9, 10.7 Hz, 2H), 3.98 (dd, *J*= 3.9, 4.7 Hz, 2H), 5.16 (d, *J*= 14.3 Hz, 2H), 5.23 (d, *J*= 14.3 Hz, 2H), 7.23 (td, *J*= 0.7, 7.5 Hz, 2 H), 7.3 (dt, *J*= 0.7, 7.5 Hz, 2H), 7.38 (dt, *J*= 0.9, 7.5 Hz, 2H), 7.76 (d, *J*= 7.5 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 24.9 (CH_2), 32.5 (CH_2), 61.0 (CH), 71.7 (CH_2), 121.1 (CH), 123.4 (CH), 128.0 (CH), 130.6 (CH), 130.9 (C), 143.1 (C), 158.9 (C) ppm.
IR (HATR): 3040, 2927, 2873, 2854, 1689, 1614, 1468, 1448, 1360, 1288, 1227, 1093, 1015, 951, 863, 775, 726, 702, 670 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 346 (M^+, 22), 213 (22), 186 (10), 160 (30), 146 (20), 118 (70), 104 (46), 90 (100), 63 (15), 41 (12).
ES-MS: 347 $[M+H]^+$.
Melting Point (℃) : 146℃.
Optical rotation: $[\alpha]_D^{20} = +\ 84.8$ (*c* 1.12, $CHCl_3$).
HRMS (EI): calcd for $C_{22}H_{22}N_2O_2$: 346.1681; found 346.1680.

6.3.3 Synthesis of (*R*)-(+)-N,N'-bis-(3*H*-isobenzofuran-1-ylidene)-1,1'-binaphthyl-2,2'-diamine (4.40).

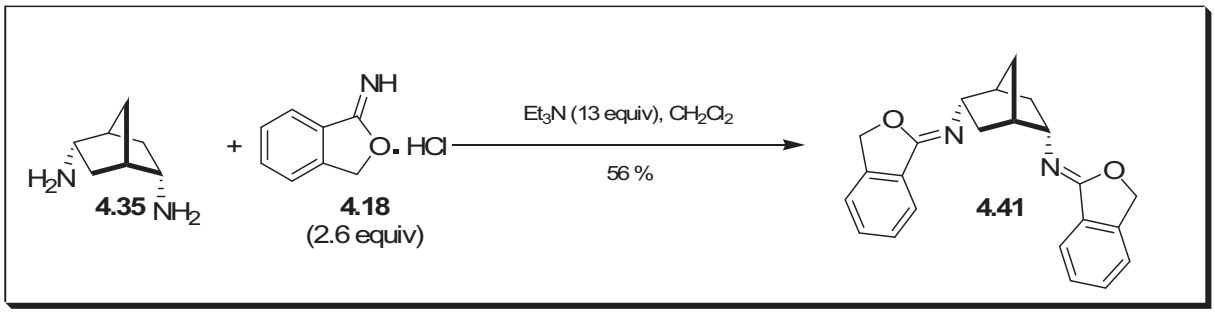


A suspension of (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine (**4.34**) (99 mg, 0.35 mmol) and imidate **4.18** (179 mg, 1.06 mmol) in MeOH (5 mL) was cooled in an ice bath. Et_3N (0.32 mL, 2.3 mmol) was added and the resulting suspension was refluxed for 5 days. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/EtOAc, 7/3, + 1% Et_3N) followed by a recrystallization in hexane/CH_2Cl_2 resulted in **4.40** as a white solid, 127.8 mg (71 %).

Formula: $C_{36}H_{24}N_2O_2$ (516.59 g/mol).
R_f (toluene/EtOAc 7/3 + 1% Et_3N): 0.50
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.07 (d, *J*= 14.6 Hz, 2H), 4.84 (d, *J*= 14.6 Hz, 2H), 7.10-7.56 (m, 16H), 7.85 (m, 4H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 71.8 (CH_2), 120.8 (CH), 122.9 (CH), 123.9 (CH), 124.6 (CH), 125.6 (CH), 126.5 (C), 126.9 (CH), 127.5 (CH), 127.6 (CH), 128.4 (CH), 130.5 (C), 130.7, 131.4 (CH), 133.8 (C), 143.2 (C), 144.3 (C), 158.3 (C) ppm.
IR (HATR): 3050, 2357, 1687, 1614, 1589, 1502, 1466, 1361, 1291, 1262, 1206, 1408, 1004, 942, 826, 770, 727 cm^{-1}.

EI-MS *m/z* (rel. intensity %): 516 (M^+, 16), 382 (29), 284 (12), 266 (18), 149 (32), 118 (31), 90 (83), 45 (100).
ES-MS: 517 $[M+H]^+$.
Melting Point (℃) : 216-218℃.
Optical rotation: $[\alpha]_D^{20} = +596.6$ (*c* 1.01, $CHCl_3$).
HRMS (EI): calcd for $C_{36}H_{24}N_2O_2$: 516.1838; found 516.1837.

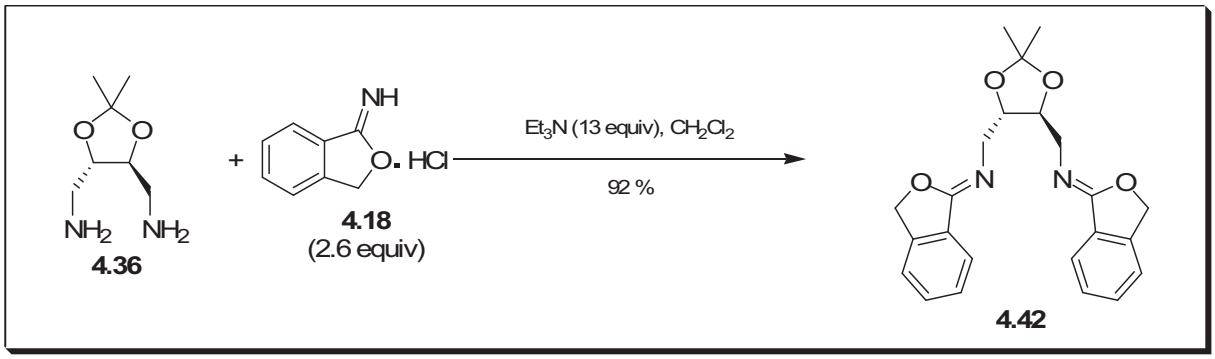
6.3.4 Synthesis of (1*S*, 2*S*, 4*S*, 5*S*)-bis-(3*H*-isobenzofuran-1-ylidene)-bicyclo[2.2.1]heptane-2,5-diamine (4.41).



A suspension of (1*S*, 4*S*)-DIANANE (**4.35**)[1] (410 mg, 3.26 mmol) and imidate **4.18** (1.60 g, 9.46 mmol) in dry CH_2Cl_2 (30 mL) was cooled in an ice bath. Et_3N (2.5 mL, 18 mmol) was added and the resulting suspension was stirred for 16h at room temperature. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/Et_2O, 6/4, 1% Et_3N) resulted in a white solid. This contained 90% of **3c** and 10% of endo-exo bisimidaat. Recrystallization in CH_2Cl_2/hexane afforded **4.41** as a pure product, 654.3 mg (56 %).

Formula: $C_{23}H_{22}N_2O_2$ (358.43 g/mol).
R_f (toluene/Et_2O, 6/4, + 1% Et_3N): 0.24
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.59 (s, 2H), 1.93 (m, 2H), 1.95 (m, 2H), 2.38 (s, 2H), 4.18 (m, 2H), 5.29 (s, 4H), 7.31 (d, *J*= 7.6 Hz, 2H), 7.35 (t, *J*= 7.6 Hz, 2H), 7.44 (t, *J*= 7.6 Hz, 2H), 7.87 (d, *J*= 7.6 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 29.8 (CH_2), 38.1 (CH_2), 43.2 (CH), 58.2 (CH), 72.1 (CH_2), 121.1 (CH), 123.8 (CH), 128.5 (CH), 130.6 (C), 131.0 (CH), 143.0 (C), 160.0 (C) ppm.
IR (HATR): 3023, 2963, 2860, 2368, 2324, 1679, 1468, 1447, 1362, 1337, 1286, 1062, 1042, 1002, 936, 850, 780, 723 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 358 (M^+, 9), 317 (9), 239 (9), 225 (24), 198 (24), 184 (32), 159 (23), 134 (27), 118 (69), 90 (100).
ES-MS: 359 $[M+H]^+$.
Melting Point (℃) : 108℃.
Optical rotation: $[\alpha]_D^{20} = -54.6$ (*c* 1.24, $CHCl_3$).
HRMS (EI): calcd for $C_{23}H_{22}N_2O_2$: 358.1681; found 358.1682.

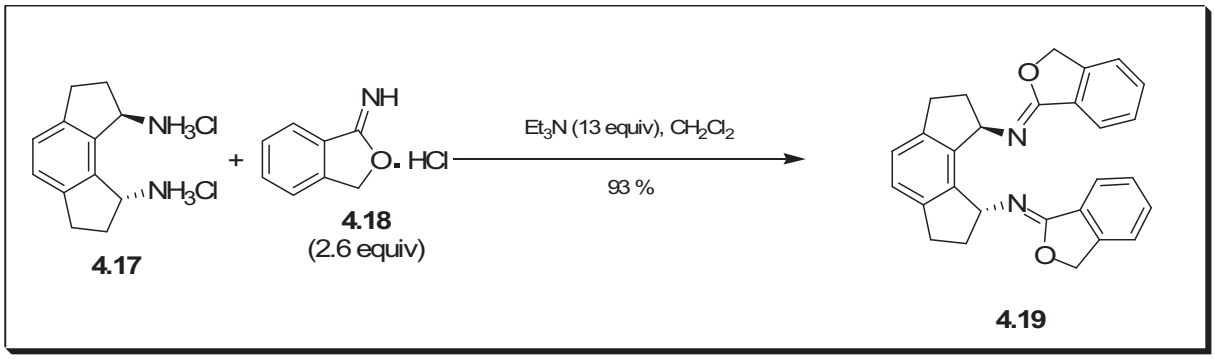
6.3.5 Synthesis of (4*S*, 5*S*)-4,5-di[(3*H*-isobenzofuran-1-ylidene)aminomethyl]-2,2-dimethyl-1,3-dioxolane (4.42).



A suspension of (4*S*, 5*S*)-4,5-di(aminomethyl)-2,2-dimethyl-1,3-dioxolane (**4.36**) (105.0 mg, 0.66 mmol) and imidate **4.18** (307 mg, 1.81 mmol) in CH_2Cl_2 was cooled in an ice bath. Et_3N (0.48 mL, 3.4 mmol) was added and the reaction mixture was stirred for 16h at room temperature. Evaporation in vacuo and recrystrallization from EtOAc resulted in **4.42** as a white solid, 236.6 mg (92 %).

Formula: $C_{23}H_{24}N_2O_4$ (392.45 g/mol).
R_f (CH_2Cl_2/MeOH 9/1): 0.76
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 6H), 3.81 (m, 4 H), 4.24 (t, *J*= 3.5 Hz, 2H), 5.25 (s, 4 H),), 7.31 (d, *J*= 7.5 Hz, 2 H), 7.37 (t, *J*= 7.5 Hz, 2H), 7.46 (dt, *J*= 1.0, 7.5 Hz, 2H), 7.83 (d, *J*= 7.5 Hz, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 27.3 (CH_3), 49.8 (CH_2), 72.1 (CH_2), 79.8 (CH), 109.1 (C), 121.2 (CH), 123.7 (CH), 128.3 (CH), 130.4 (C), 131.1 (CH), 143.2 (C), 160.7 (C) ppm.
IR (HATR): 2903, 1692, 1367, 1293, 1251, 1166, 1073, 998, 724, 664 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 392 (M^+, <1), 377 (2), 260 (5), 246 (17), 201 (29), 188 (46), 160 (17), 146 (100), 118 (28), 91 (58).
ES-MS: 393 $[M+H]^+$.
Melting Point (℃) : 204℃.
Optical rotation: $[\alpha]_D^{20} = -47.0$ (*c* 1.00, $CHCl_3$).
HRMS (EI): calcd for $C_{23}H_{24}N_2O_4$: 392.1736; found 392.1737.

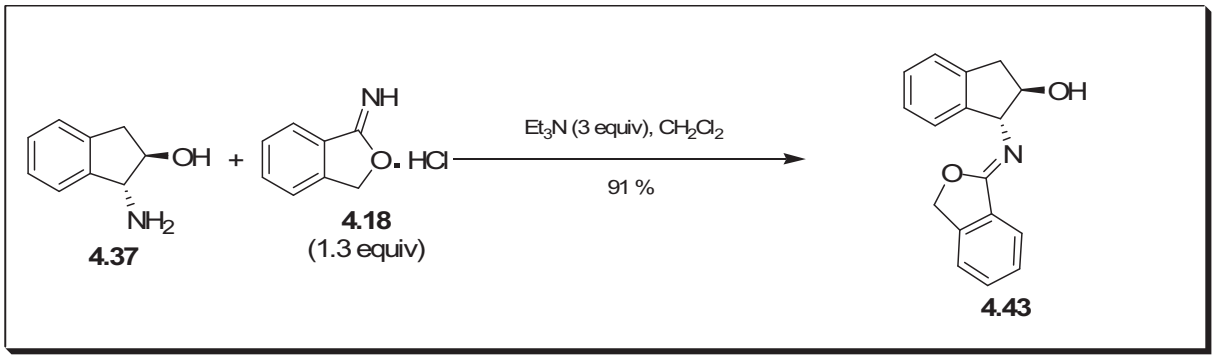
6.3.6 Synthesis of (1*R*, 8*R*)-N,N'-Bis-(3*H*-isobenzofuran-1-ylidene)-1,2,3,6,7,8-hexahydro-*as*-indacene-1,8-diamine (4.19).



(1*R*, 8*R*)-1,2,3,6,7,8-hexahydro-*as*-indacene-1,8-diamine hydrochloride (**4.17**)[2] (10.9 mg, 0.0417 mmol) and imidate **4.18** (20.3 mg, 0.1197 mmol) was suspended in dry CH_2Cl_2 (0.75 mL) and cooled in an ice bath. Et_3N (32 µL, 0.230 mmol) was added and the resulting suspension was stirred for 24 h at room temperature. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (cyclohexane/EtOAc, 2/1) resulted in **4.19** as a white solid, 16.3 mg (93 %).

Formula: $C_{28}H_{24}N_2O_2$ (420.50 g/mol).
R_f (hexane/EtOAc 2/1): 0.19
^{1}H-NMR (300 MHz, C_6D_6): δ 2.20 (dddd, *J*= 8.0, 8.5, 8.5, 12.1 Hz, 2H), 2.64 (dddd, *J*= 2.2, 8.0, 8.5, 12.1 Hz, 2H), 2.86 (ddd, *J*= 8.5, 8.5, 15.0 Hz, 2H), 3.01 (ddd, *J*= 2.2, 8.5, 15.0 Hz, 2H), 3.44 (d, *J*= 14.2 Hz, 2H), 4.28 (d, *J*=14.2 Hz, 2H), 6.23 (t, *J*= 8.0 Hz, 2H), 6.37-6.45 (m, 2H), 6.85-6.98 (m, 4H), 7.18 (s, 2H), 7.94-8.01 (m, 2H) ppm.
^{13}C-NMR (75.4 MHz, C_6D_6): δ 31.4 (CH_2), 34.7 (CH_2), 60.8 (CH), 71.0 (CH_2), 120.7 (CH), 123.5 (CH), 123.9 (CH), 127.8 (CH), 130.2 (CH), 131.9 (C), 142.2 (C), 143.5 (C), 143.7 (C), 158.2 (C) ppm.
IR (HATR): 2952, 2936, 2874, 2844, 1695, 1468, 1364, 1338, 1290, 1228, 1152, 1078, 1025, 1016, 775, 726 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 421 (M^+, <1), 287 (100), 258 (11), 154 (20), 90 (21).
ES-MS: 421 $[M+H]^+$.
Melting Point (℃) : 184-186 ℃.
Optical rotation: $[\alpha]_D^{20}$ = - 157.3 (*c* 0.56, $CHCl_3$).
HRMS (EI): calcd for $C_{28}H_{24}N_2O_2$: 420.1838; found 420.1830.

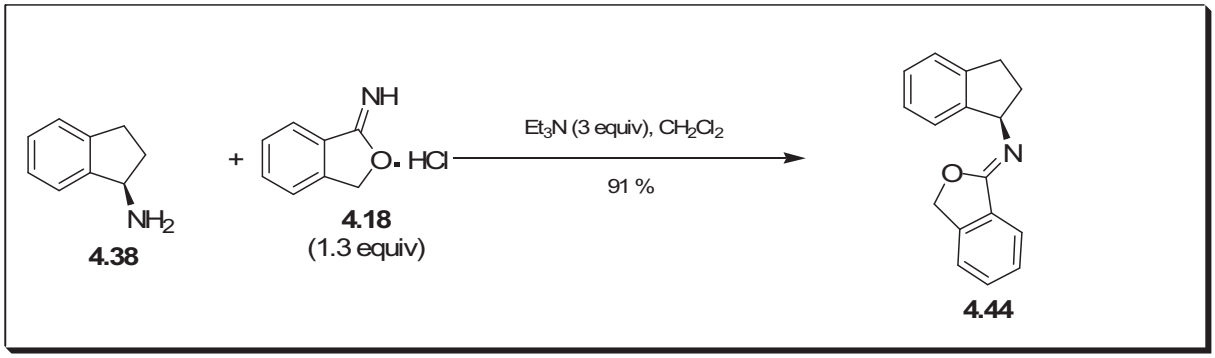
6.3.7 Synthesis of (1*R*, 2*R*)- *trans*- 1-(3*H*-isobenzofuran-1-ylideneamino)-indan-2-ol (4.43).



A suspension of (1*R*, 2*R*)-(-)-*trans*-1-amino-2-indanol (**4.37**) (100.0 mg, 0.67 mmol) and imidate **4.18** (125.0 mg, 0.74 mmol) in CH_2Cl_2 was cooled in an ice bath. Et_3N (0.28 mL, 2.0 mmol) was added and the reaction mixture was stirred for 48h at room temperature. Evaporation in vacuo and recrystrallization from CH_2Cl_2 resulted in **4.43** as a white solid, 161 mg (91 %).

Formula: $C_{17}H_{15}NO_2$ (265.31 g/mol).
R_f (CH_2Cl_2/MeOH 9/1): 0.58
^{1}H-NMR (300 MHz, DMSO): δ 2.74 (dd, *J*= 7.0, 15.6 Hz, 1H), 3.18 (dd, *J*= 7.0, 15.6 Hz, 1H), 4.33 (m, *J*= 5.6, 7.0 Hz, 1H), 5.12 (d, *J*= 5.6 Hz, 1H), 5.16 (d, *J*= 5.2 Hz, 1H), 5.44 (d, *J*= 14.9 Hz, 1H), 5.50 (d, *J*= 14.9 Hz, 1H), 7.05-7.20 (m, 4H), 7.44-7.49 (m, 1H), 7.56-7.63 (m, 2H), 7.70 (d, *J*= 7.6Hz, 1H) ppm.
^{13}C-NMR + HSQC (75.4 MHz, DMSO): δ 39.3 (CH_2), 68.3 (CH), 72.1 (CH_2), 79.5 (CH), 122.2 (CH), 122.8 (CH), 124.3 (CH), 124.5 (CH), 126.4 (CH), 127.1 (CH), 128.4 (CH), 129.7 (C), 131.5 (CH), 140.2 (C), 143.2 (C), 143.8 (C), 160.1 (C) ppm.
IR (HATR): 3189, 1680, 1467, 1419, 1369, 1298, 1225, 1200, 1084, 1028, 998, 777, 747, 730, 703, 675 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 265 (M^+, 20), 247 (4), 237 (17), 218 (5), 146 (15), 134 (23), 118 (100), 104 (50), 90 (97), 63 (19), 49 (43).
ES-MS: 266 $[M+H]^+$.
Melting Point (℃) : 236 ℃.
Optical rotation: $[\alpha]_D^{20} =$ - 304.8 (*c* 0.81, DMSO).
HRMS (EI): calcd for $C_{17}H_{15}NO_2$: 265.1103; found 265.1107.

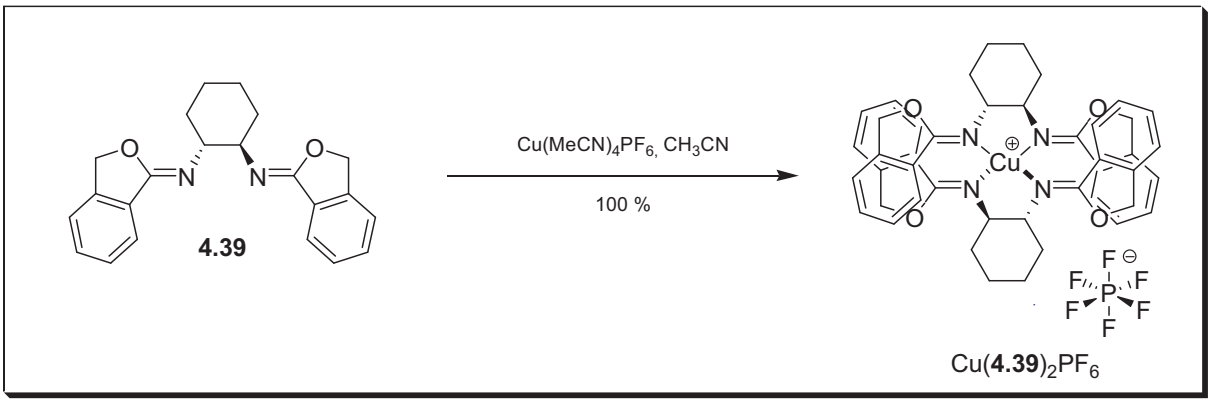
6.3.8 Synthesis of (*R*)-indan-1-yl-(3*H*-isobenzofuran-1-ylidene)-amine (4.44).



A suspension of (*R*)-(-)-1-indanylamine (**4.38**) (100 mg, 0.75 mmol) and imidate **4.18** (178.0 mg, 1.05 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (0.31 mL, 2.25 mmol) was added and the resulting suspension was stirred for 24h at room temperature. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/Et_2O, 6/4, + 1% Et_3N) resulted in **4.44** as a white solid, 138 mg (74 %).

Formula: $C_{17}H_{15}NO$ (249.31 g/mol).
R_f (CH_2Cl_2/MeOH 9/1): 0.79
^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.09-2.21 (m, *J*= 7.5, 8.7, 12.5 Hz, 1H), 2.59-2.64 (m, *J*= 3.2, 7.5, 12.5 Hz, 1H), 2.93-3.04 (m, *J*= 15.7 Hz, 1H), 3.11-3.20 (ddd, *J*= 3.2, 8.8, 15.7 Hz, 1H), 5.42 (s, 2H), 5.57 (dd, *J*= 7.5, 7.5 Hz, 1H), 7.20-7.45 (m, 5H), 7.48 (d, *J*= 7.5 Hz, 1H), 7.55 (t, *J*=7.5 Hz, 1H), 7.96 (d, *J*= 7.5 Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 30.8 (CH_2), 34.6 (CH_2), 61.2 (CH), 72.0 (CH_2), 121.2 (CH), 123.6 (CH), 124.2 (CH), 124.4 (CH), 126.2 (CH), 126.8 (CH), 128.3 (CH), 130.5 (C), 131.1 (CH), 143.1 (C), 143.4 (C), 145.8 (C), 160.1 (C) ppm.
IR (HATR): 3018, 2957, 2931, 2859, 1689, 1470, 1456, 1361, 1331, 1289, 1073, 1024, 1015, 1002, 781, 776, 766, 740, 726, 700, 670 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 249 (M^+, 20), 234 (11), 220 (13), 134 (100), 118 (64), 90 (80), 76 (16), 63 (27), 51 (21).
ES-MS: 250 $[M+H]^+$.
Melting Point (℃) : 79-80 ℃.
Optical rotation: $[\alpha]_D^{20} =$ + 123.5 (*c* 0.78, $CHCl_3$).
HRMS (EI): calcd for $C_{17}H_{15}NO$: 249.1154; found 249.1154.

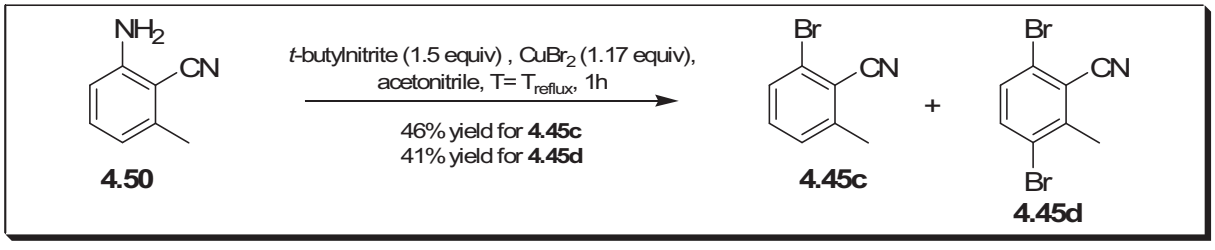
6.3.9 Synthesis of $Cu(4.39)_2PF_6$.



N,N'-Bis-(3*H*-isobenzofuran-1-ylidene)-cyclohexane-(1*R*, 2*R*)-diamine **(4.39)** (31.0 mg, 89.5 µmol) and $Cu(MeCN)_4PF_6$ (29.4 mg, 78.9 µmol) were dissolved in acetonitrile (2 mL). The resulting yellow suspension was filtrated and evaporated in vacuo. The resulting yellow solids were recrystallized from benzene. This resulted in pure $Cu(\mathbf{3a})_2PF_6$ as a yellow solid, 40.3 mg (quantitative yield).

Formula: $C_{44}H_{44}CuF_6N_4O_4P$ (901.35 g/mol).
^{1}H-NMR (300 MHz, CD_3CN): δ 1.20 (m, 8H), 1.68 (m, 4H), 2.31 (d, *J*= 10.4 Hz, 4H), 3.20 (br s, 4H), 4.83 (d, *J*= 15.4 Hz, 4H), 5.23 (d, *J*= 15.4 Hz, 4H), 7.42 (m, 8H), 7.58 (t, *J*= 7.5 Hz, 4H), 8.27 (d, *J*= 7.5 Hz, 4H) ppm.
^{13}C-NMR (75.4 MHz, CD_3CN): δ 26.0 (CH_2), 31.7 (CH_2), 64.0 (CH), 75.2 (CH_2), 122.8 (CH), 125.4 (CH), 129.3 (CH), 130.0 (C), 133.5 (CH), 144.8(C), 167.0 (C) ppm.
IR (HATR): 2937, 2861, 1644, 1470, 1452, 1364, 1298, 1102, 1095, 1040, 1020, 998, 953, 832, 776, 726, 673 cm^{-1}.
ES-MS: 755 $[Cu(\mathbf{3a})_2]^+$, 450 $[Cu(\mathbf{3a})\ CH_3CN]^+$, 409 $[Cu(\mathbf{3a})]^+$, 347 $[\mathbf{3a}+H]^+$.
Melting Point (℃) : decomposition.
Optical rotation: $[\alpha]_D^{20} =$ - 387.3 (*c* 0.79, CH_3CN).

6.3.10 Synthesis of 2-bromo-6-methylbenzonitrile (4.45c)



2-amino-6-methylbenzonitrile **4.50** (10.18 g, 77.0 mmol) was added slowly over 5 min to a suspension of *t*-butyl nitrite (13.5 mL, 114.0 mmol) and anhydrous copper (II) bromide (20.28 g, 90 mmol) in 300 mL anhydrous acetonitrile. The resulting suspension was heated at 65℃. After 1h the black r eaction mixture was cooled to room temperature, poured out into 800 mL 1N HCl solution and extracted with CH_2Cl_2 (3x 800 mL). The combined organic phases were dried over $MgSO_4$ and

concentrated in vacuo. The resulting brown solids were purified by flash chromatography over silicagel (hexane/EtOAc, 97/3) resulting in pure **4.45c** (6.84 g, 46%). Formation of 2,5-dibromo-6-methylbenzonitrile **4.45d** (8.58 g, 41%) was also observed.

For **4.45c**:

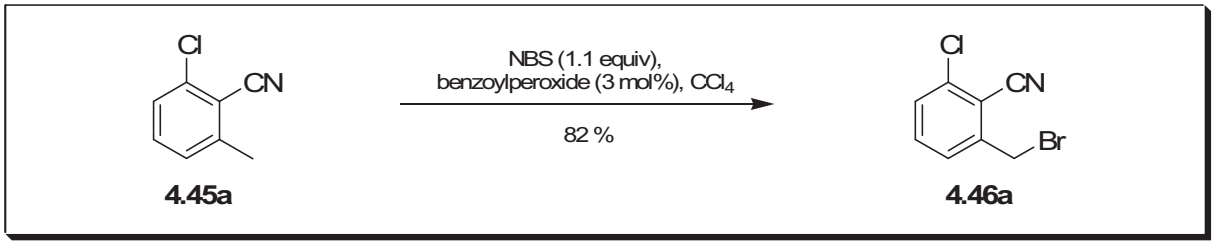
Formula: C_8H_6BrN (196.04 g/mol).
R_f (hexane/EtOAc 9/1): 0.27
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 7.25 (d, *J*= 7.7Hz, 1H), 7.31 (t, *J*= 7.7Hz, 1H), 7.48 (d, *J*= 7.7Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 21.2 (CH_3), 116.2 (C), 116.4 (C), 125.5 (C), 128.8 (CH), 130.3 (CH), 133.2 (CH), 144.7 (C) ppm.
IR (HATR): 3074, 2924, 2228, 1590, 1556, 1491, 1452, 1381, 1272, 1202, 1175, 1137, 1035, 998, 924, 843, 783, 719 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 197 (M^+, 36), 195 (M^+, 39), 116 (87), 89 (45), 75 (12), 63 (31), 49 (100).
Melting Point (℃) : 91 ℃.
HRMS (EI): calcd for $C_8H_6{}^{79}BrN$: 194.9684; found 194.9691.

For **4.45d**:

Formula: $C_8H_5Br_2N$ (274.94 g/mol).
R_f (hexane/EtOAc 9/1): 0.38
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H), 7.36 (d, *J*= 8.7Hz, 1H), 7.59 (d, *J*= 8.7Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 22.5 (CH_3), 115.9 (C), 117.6 (C), 124.1 (C), 124.5 (C), 131.4 (CH), 137.2 (CH), 144.0 (C) ppm.
IR (HATR): 3098, 3065, 2953, 2923, 2853, 2226, 1567, 1431, 1389, 1379, 1264, 1210, 1196, 1136, 1006, 852, 814 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 275 (M^+, 31), 194 (25), 114 (32), 84 (45), 49 (100).
Melting Point (℃) : 119 ℃.
HRMS (EI): calcd for $C_8H_5{}^{79}Br_2N$: 272.8789; found 272.8792.

6.3.11 A typical procedure for the preparation of the substituted 2-(bromomethyl)benzonitriles (4.46)

6.3.11.1 Synthesis of 2-chloro-6-(bromomethyl)benzonitrile (4.46a)



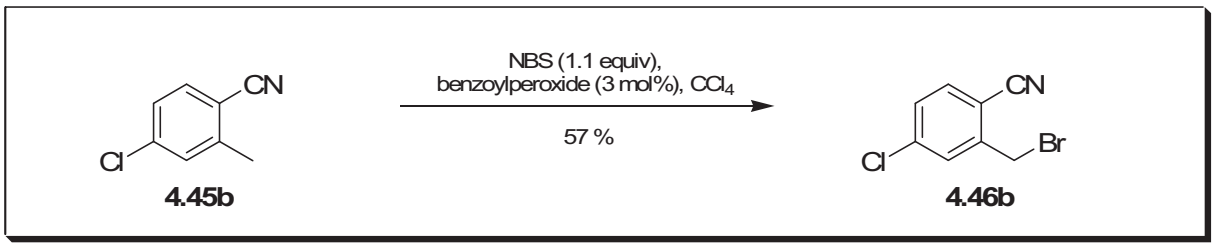
4.45a **4.46a**

A solution of 2-chloro-6-methylbenzonitrile **4.45a** (4.83 g, 31.9 mmol), NBS (6.24 g, 35.1 mmol) and benzoylperoxide (232.0 mg, 0.96 mmol) in CCl_4 (100 mL) was

refluxed for 7 h. Afterwards, the solids are filtered off and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (pentane/ Et_2O, 90/10) resulting in pure **4.46a**, 4.35 g (82%). No formation of the dibromo product **4.47a** was observed.

Formula: C_8H_5BrClN (230.49 g/mol).
R_f (pentane/Et_2O 9/1): 0.18
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.60 (s, 2H), 7.43-7.54 (m, 3H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 28.9 (CH_2), 113.4 (C), 113.9 (C), 128.5 (CH), 129.7 (CH), 133.7 (CH), 137.7 (C), 143.4 (C) ppm.
IR (HATR): 3070, 3025, 2227, 1588, 1567, 1455, 1443, 1264, 1219, 1203, 1180, 1155, 1117, 988, 905, 796, 780, 737, 628, 609 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 231 (M^+, 10), 229 (M^+, 8), 152 (33), 150 (100), 123 (27), 114 (22), 81 (18), 79 (18), 63 (21), 50 (14).
Melting Point (℃) : 83 ℃.
HRMS (EI): calcd for $C_8H_5N^{35}Cl^{79}Br$: 228.9294; found 228.9307.

6.3.11.2 2-(bromomethyl)-4-chlorobenzonitrile (4.46b)

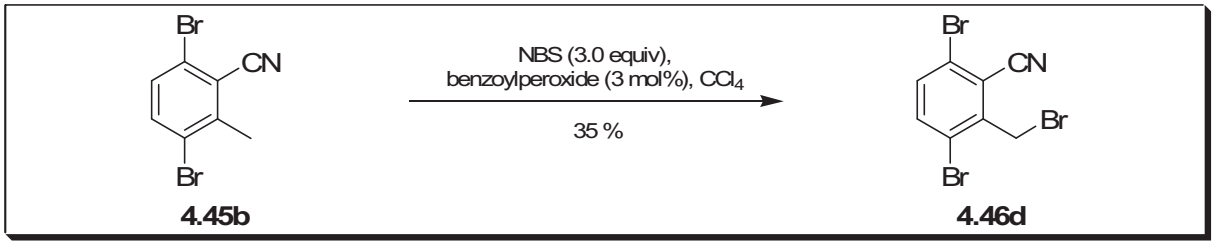


4.45b **4.46b**

The reaction was performed on 4-chloro-2-methylbenzonitrile **4.45b** (2.0 g, 13.2 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (pentane/Et_2O, 96/4) resulting in pure **4.46b**, 1.74 g (57%). Formation of the dibromo product **4.47b** was also observed, 0.97 g (24%).

Formula: C_8H_5BrClN (230.49 g/mol).
R_f (pentane/Et_2O 9/1): 0.29
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.57 (s, 2H), 7.39 (dd, *J*= 2.0, 8.3Hz, 1H), 7.55 (d, *J*= 2.0Hz, 1H), 7.59 (d, *J*= 8.3Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 28.2 (CH_2), 110.8 (C), 116.0 (C), 129.4 (CH), 130.8 (CH), 134.2 (CH), 139.7 (C), 142.8 (C) ppm.
IR (HATR): 3080, 3035, 2224, 1592, 1564, 1480, 1438, 1404, 1284, 1230, 1222, 1180, 1105, 1080, 900, 882, 827, 742, 726, 630, 618 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 233 (M^+, 25), 231 (M^+, 100), 229 (M^+, 77), 203 (9), 152 (6), 150 (18), 114 (66), 87 (31), 63 (35).
Melting Point (℃) : 78 ℃.
HRMS (EI): calcd for $C_8H_5N^{35}Cl^{79}Br$: 228.9294; found 228.9287.

6.3.11.3 2-(bromomethyl)-3,6-dibromobenzonitrile (4.46d)



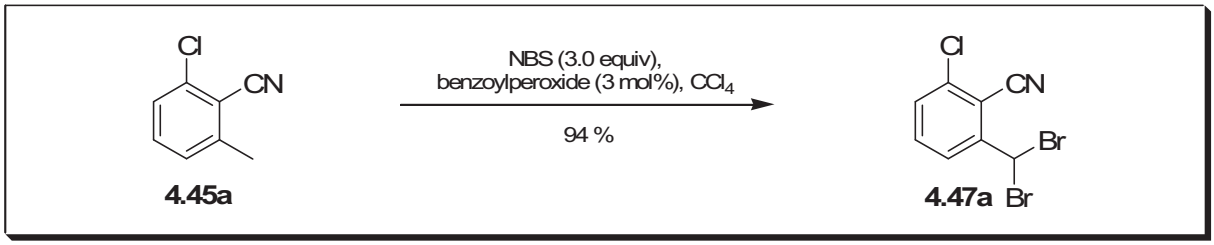
A solution of 2,5-dibromo-6-methylbenzonitrile **4.45d** (7.00 g, 25.5 mmol), NBS (13.62 g, 76.5 mmol) and benzoylperoxide (204.0 mg, 0.84 mmol) in CCl_4 (71 mL) was refluxed for 16 h. Afterwards, the solids are filtered off and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (hexane/ Et_2O, 95/5) resulting in pure **4.46d**, 3.12 g (35%). Only a marginal formation of the dibromo product **4.47d** was observed.

Formula: $C_8H_4Br_3N$ (353.84 g/mol).
R_f (hexane/EtOAc 95/5): 0.19
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.76 (s, 2H), 7.48 (d, *J*= 8.6Hz, 1H), 7.65 (d, *J*= 8.6Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 29.8 (CH_2), 114.7 (C), 117.7 (C), 124.0 (C), 125.4 (C), 133.9 (CH), 138.2 (CH), 142.6 (C) ppm.
IR (HATR): 3055, 3040, 2922, 2852, 2233, 1559, 1434, 1393, 1277, 1225, 1198, 1156, 1148, 1122, 1101, 896, 827, 806, 798, 753, 740 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 353 (8), 274 (100), 195 (29), 193 (29), 114 (83), 88 (50), 63 (44), 49 (82).
Melting Point (℃) : 163-165℃.

6.3.12 A typical procedure for the preparation of the substituted 2-(dibromomethyl)benzonitriles (4.47)

2-(dibromomethyl)benzonitriles (**4.47**) were synthesized according to a literature procedure.[3]

6.3.12.1 Synthesis of 2-chloro-6-(dibromomethyl)benzonitrile (4.47a).

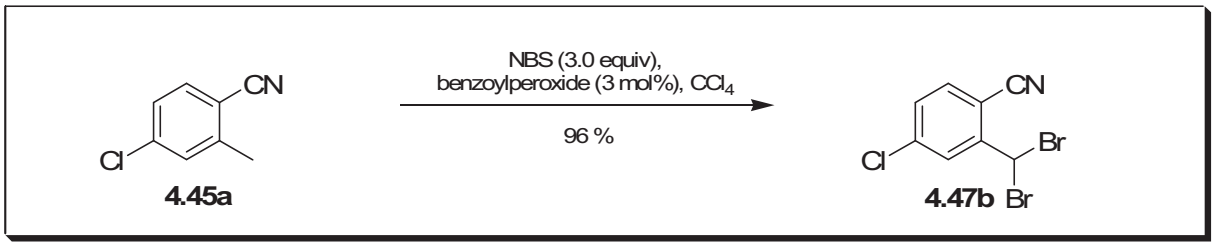


A solution of 2-chloro-6-methylbenzonitrile **4.45a** (9.91 g, 65.4 mmol), NBS (35.22 g, 197.9 mmol) and benzoylperoxide (534.0 mg, 2.2 mmol) in CCl_4 (100 mL) was refluxed overnight. Afterwards, the solids are filtered off and the filtrate was

concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (hexane/ EtOAc, 95/5) resulting in pure **4.47a**, 19.04 g (94%).

Formula: $C_8H_4Br_2ClN$ (309.39 g/mol).
R_f (hexane/EtOAc 95/5): 0.20
^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 1H), 7.49 (dd, *J*= 0.8, 8.1Hz, 1H), 7.62 (t, *J*= 8.1 Hz, 1H), 7.94 (dd, *J*= 0.8, 8.1Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 35.0 (CH), 109.5 (C), 113.1 (C), 128.0 (CH), 130.6 (CH), 134.1 (CH), 136.9 (C), 146.3 (C) ppm.
IR (HATR): 3076, 3008, 2232, 1589, 1567, 1454, 1439, 1292, 1251, 1238, 1174, 1140, 1134, 891, 796, 779, 735, 651, 633 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 309 (M^+, 2), 232 (25), 230 (100), 228 (74), 149 (14), 114 (39), 87 (17), 74 (9), 63 (16), 50 (13).
Melting Point (℃) : 120 ℃.
HRMS (EI): calcd for $C_8H_4N^{35}Cl^{79}Br_2$: 306.8399; found 306.8386.

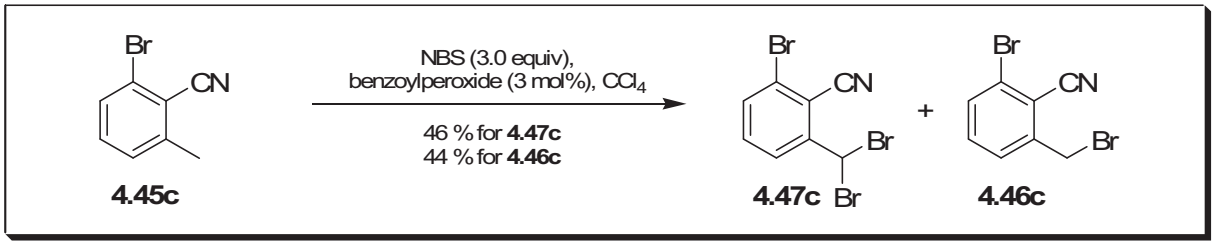
6.3.12.2 Synthesis of 2-(dibromomethyl)-4-chlorobenzonitrile (4.47b).



The reaction was performed on 4-chloro-2-methylbenzonitrile **4.45a** (9.80 g, 64.6 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (hexane/ EtOAc, 95/5) resulting in pure **4.47b**, 19.55 g (96%).

Formula: $C_8H_4Br_2ClN$ (309.39 g/mol).
R_f (hexane/EtOAc 95/5): 0.24
^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 7.41 (dd, *J*= 2.0, 8.4Hz, 1H), 7.55 (d, *J*= 8.4Hz, 1H), 8.00 (d, *J*= 2.0, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 34.3 (CH), 106.9 (C), 115.2 (C), 130.4 (CH), 130.6 (CH), 133.5 (CH), 140.5 (C), 145.9 (C) ppm.
IR (HATR): 3080, 3058, 3028, 3004, 2359, 2227, 1589, 1556, 1481, 1462, 1404, 1304, 1279, 1206, 1170, 1138, 1114, 1081, 902, 820, 742, 689, 649, 622 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 309 (M^+, 2), 232 (25), 230 (100), 228 (73), 149 (16), 114 (47), 87 (20), 74 (10), 63 (20), 50 (15).
Melting Point (℃) : 120 ℃.
HRMS (EI): calcd for $C_8H_4N^{35}Cl^{79}Br_2$: 306.8399; found 306.8386.

6.3.12.3 Synthesis of 2-bromo-6-(dibromomethyl)benzonitrile (4.47c).



The reaction was performed on 2-bromo-6-methylbenzonitrile **4.45c** (1.0 g, 5.1 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (hexane/ EtOAc, 95/5) resulting in pure **4.47c**, 825.0 mg (46%). Formation of the monobrominated product **4.46c** was also observed, 616.7 mg (44%).

For **4.47c**:

Formula: $C_8H_4Br_3N$ (353.84 g/mol).
R_f (hexane/EtOAc 95/5): 0.24
^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.98 (s, 1H), 7.54 (*J*= 7.9Hz, 1H), 7.66 (d, *J*= 7.9 Hz, 1H), 7.99 (d, *J*= 7.9Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 35.2 (CH), 111.8 (C), 114.3 (C), 125.3 (C), 128.6 (CH), 133.9 (CH), 134.3 (CH), 146.7 (C) ppm.
IR (HATR): 3072, 3010, 2228, 1586, 1557, 1449, 1434, 1319, 1289, 1244, 1233, 1198, 1174, 1144, 1118, 868, 792, 732, 648 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 355 (M^+, <5), 353 (M^+, <5), 274 (100), 114 (62), 88 (25), 63 (25).
Melting Point (℃) : 116 ℃.
HRMS (EI): calcd for $C_8H_4{}^{79}Br_3N$: 350.7894; found 350.7886.

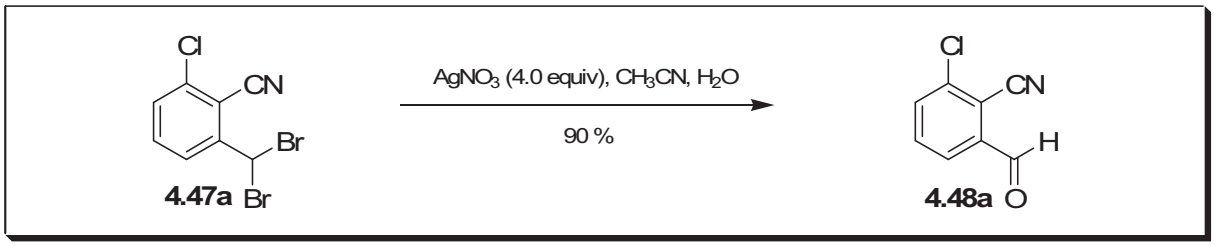
For **4.46c**:

Formula: $C_8H_5Br_2N$ (274.94 g/mol).
R_f (hexane/EtOAc 95/5): 0.12
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.62 (s, 2H), 7.43 (t, *J*= 7.8Hz, 1H), 7.49 (d, *J*= 7.8 Hz, 1H), 7.63 (d, *J*= 7.8Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 29.2 (CH_2), 115.1 (C), 115.8 (C), 126.3 (C), 129.0 (CH), 132.9 (CH), 133.8 (CH), 143.7 (C) ppm.
IR (HATR): 3079, 3066, 3029, 2977, 2953, 2925, 2872, 2232, 1718, 1581, 1559, 1446, 1438, 1312, 1285, 1260, 1222, 1201, 1177, 1150, 1110, 894, 857, 798, 767, 739, 621 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 275 (M^+, 9), 196 (98), 194 (100), 115 (52), 88 (24), 79 (15), 62 (22), 49 (18).
Melting Point (℃) : 126 ℃.
HRMS (EI): calcd for $C_8H_5{}^{79}Br_2N$: 272.8789; found 272.8778.

6.3.13 A typical procedure for the preparation of the substituted 2-formylbenzonitriles (4.48)

2-formylbenzonitriles (**4.48**) were synthesized according to a literature procedure.[3]

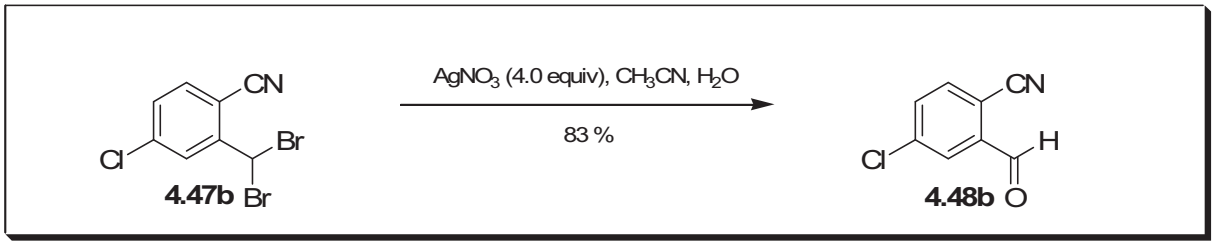
6.3.13.1 Synthesis of 2-chloro-6-formylbenzonitrile (4.48a)



To a solution of **4.47a** (18.0 g, 58.2 mmol) in CH_3CN (60 mL) was added a solution of $AgNO_3$ (39.5 g, 233 mmol) in H_2O (32 mL). The resulting yellow suspension was refluxed during 20 min. The solids were filtered off and washed with CH_2Cl_2 (150 mL). The combined filtrate was washed with H_2O (25 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (hexane/EtOAc, 2/1) resulting in pure **4.48a**, 8.67 g (90%).

Formula: C_8H_4ClNO (165.58 g/mol).
R_f (hexane/EtOAc 2/1): 0.36
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (t, *J*= 7.9Hz, 1H), 7.79 (dd, *J*= 1.2, 7.9Hz, 1H), 7.94 (dd, *J*= 1.2, 7.9Hz, 1H), 10.31 (s, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 112.9 (C), 114.4 (C), 127.5 (CH), 133.8 (CH), 134.9 (CH), 138.5 (C), 139.0 (C), 187.6 (CH) ppm.
IR (HATR): 3069, 2865, 2221, 1697, 1584, 1566, 1443, 1395, 1291, 1224, 1195, 1182, 1155, 922, 798, 781, 726, 675 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 167 (5); 165 (15), 139 (33), 137 (100), 110 (24), 101 (44), 84 (13), 75 (79), 61 (23), 50 (45).
Melting Point (℃) : 140 ℃.
HRMS (EI): calcd for $C_8H_4NO^{35}Cl$: 164.9981; found 164.9969.

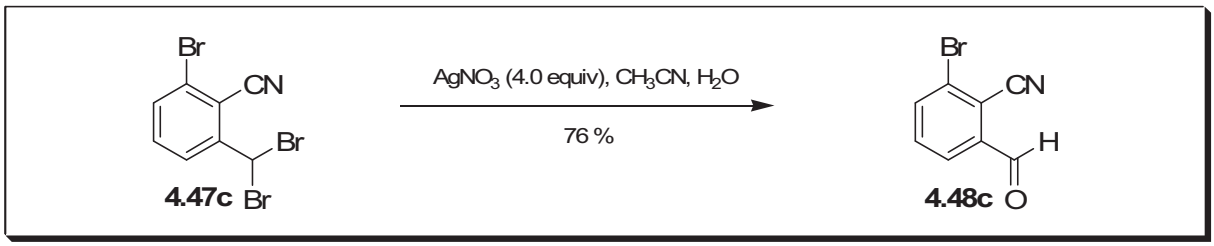
6.3.13.2 Synthesis of 2-formyl-4-chlorobenzonitrile (4.48b)



The reaction was performed on **4.47b** (18.07 g, 58.4 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (hexane/EtOAc, 9/1) resulting in pure **4.48b**, 8.04 g (83%).

Formula: C_8H_4ClNO (165.58 g/mol).
R_f (pentane/EtOAc 85/15): 0.32
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.71 (dd, *J*= 2.0, 8.3Hz, 1H), 7.77 (d, *J*= 8.3Hz, 1H), 8.00 (d, *J*= 2.0Hz, 1H), 10.31 (s, 1H) ppm.
^{13}C-NMR (75.4 MHz, C_6D_6): δ 111.9 (C), 115.2 (C), 129.2 (CH), 133.3 (CH), 134.6 (CH), 138.0 (C), 139.3 (C), 186.2 (CH) ppm.
IR (HATR): 3101, 3069, 2871, 2226, 1698, 1584, 1558, 1485, 1376, 1294, 1203, 1119, 1099, 897, 839, 744, 702, 620 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 167 (10); 165 (29), 139 (33), 137 (100), 110 (26), 102 (44), 100 (33), 75 (55), 61 (16), 50 (39).
Melting Point (℃) : 119 ℃.
HRMS (EI): calcd for $C_8H_4NO^{35}Cl$: 164.9981; found 164.9988.

6.3.13.3 Synthesis of 2-bromo-6-formylbenzonitrile (4.48c)

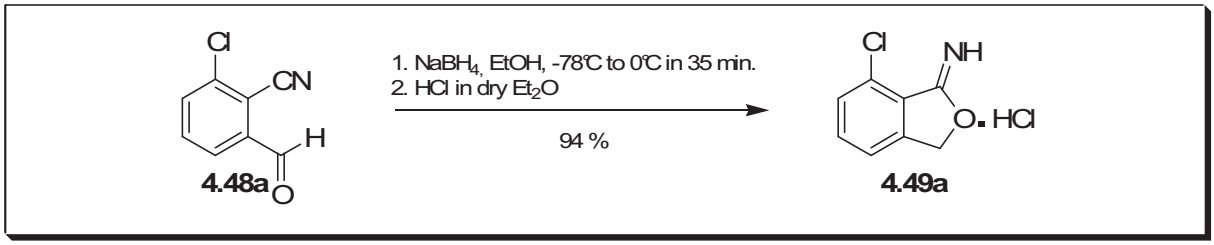


The reaction was performed on **4.47c** (1.35 g, 3.8 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (hexane/EtOAc, 8/2) resulting in pure **4.48c**, 603.0 mg (76%).

Formula: C_8H_4BrNO (210.03 g/mol).
R_f (hexane/EtOAc 2/1): 0.33
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.64 (t, *J*= 7.9Hz, 1H), 7.95 (d, *J*= 7.9Hz, 1H), 7.98 (d, *J*= 7.9 Hz, 1H), 10.29 (s, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 114.1 (C), 116.9 (C), 127.6 (C), 127.9 (CH), 133.9 (CH), 138.0 (CH), 187.7 (CH) ppm.
IR (HATR): 3078, 2921, 2854, 1698, 1641, 1579, 1557, 1436, 1390, 1279, 1219, 1176, 1134, 892, 847, 786, 722, 666 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 211 (M^+, 12), 209 (M^+, 13), 183 (93), 181 (94), 102 (100), 84 (11), 75 (93), 61 (12), 50 (53).
Melting Point (℃) : 124 ℃.
HRMS (EI): calcd for $C_8H_4{}^{79}BrNO$: 208.9476; found 208.9474.

6.3.14 A typical procedure for the preparation of the substituted imidate esters. (4.49)

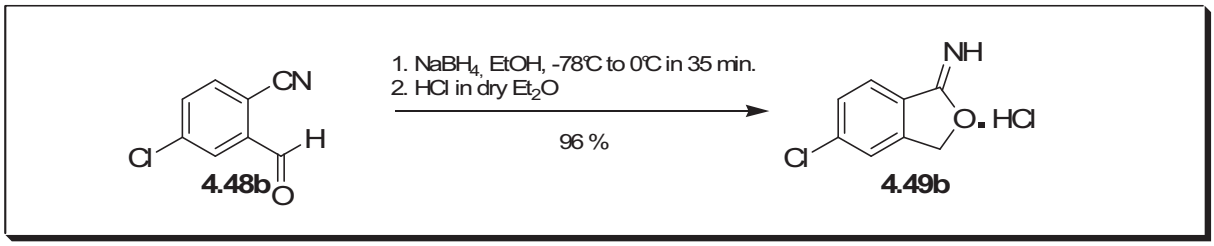
6.3.14.1 Synthesis of 7-chloro-1,3-dihydro-iminoisobenzofuran hydrochloride (4.49a).



2-Cyanobenzaldehyde **4.48a** (2 g, 12.1 mmol) was dissolved in absolute ethanol (120 mL) and cooled to -78°C. $NaBH_4$ (456.8 mg, 12.1 mmol) was added and the reaction mixture was allowed to warm to 0°C in 30 min. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3 x 500 mL). The organic phases were dried over Na_2SO_4 and concentrated in vacuo. The resulting white solid was dissolved in dry CH_2Cl_2 (40 mL) and dry HCl in Et_2O (15 mL) was added. The resulting suspension was filtrated and the white crystals were washed with dry THF. This resulted in 2.3 g (94 %) of imidate hydrochloride **4.49a**.

Formula: $C_8H_7Cl_2NO$ (204.05 g/mol).
R_f (CH_2Cl_2/MeOH 90/10): 0.64
^{1}H-NMR (300 MHz, DMSO-*d*6) δ 5.93 (s, 2H), 7.78 (d, *J*= 7.8Hz, 1H), 7.80 (d, *J*= 7.8Hz, 1H), 7.94 (t, *J*= 7.8Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, DMSO-*d*6): δ 78.0 (CH_2), 121.1 (C), 121.8 (CH), 130.3 (CH), 130.5 (C), 137.9 (CH), 150.3 (C), 173.6 (C) ppm.
IR (HATR): 3053, 2936, 2861, 2706, 2628, 2545, 2436, 1662, 1610, 1582, 1524, 1474, 1430, 1408, 1322, 1306, 1228, 1196, 1156, 1132, 1060, 1042, 919, 857, 792, 763, 727, 654 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 169 (M^+,11), 167 (M^+, 33), 140 (33), 138 (100), 111 (10), 102 (47), 89 (74), 75 (69), 63 (42), 50 (50), 43 (19).
ES-MS: 168 $[M\text{-}Cl^-]^+$.
Melting Point (°C) : decomposition.
HRMS (EI): calcd for $C_8H_6NO^{35}Cl$: 167.0138; found 167.0153.

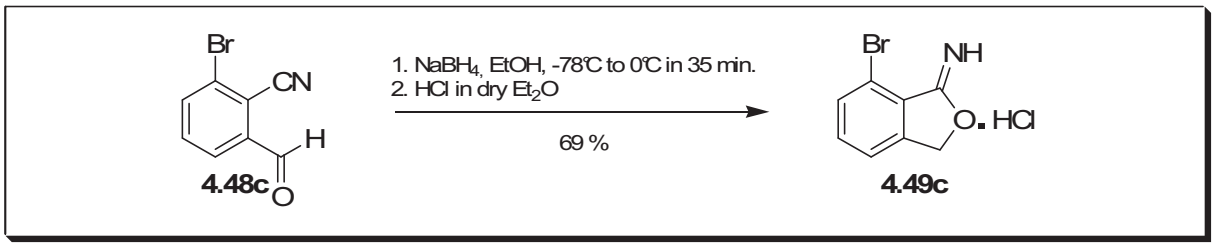
6.3.14.2 Synthesis of 5-chloro-1,3-dihydro-iminoisobenzofuran hydrochloride (4.49b).



The reaction was performed on 2-formyl-5-chlorobenzonitrile (**4.48b**) (2.0 g, 12.1 mmol) according to the typical procedure resulting in 2.38 g (96 %) of imidate ester hydrochloride (**4.49b**).

Formula: $C_8H_7Cl_2NO$ (204.05 g/mol).
R_f (CH_2Cl_2/MeOH 90/10): 0.61
^{1}H-NMR (300 MHz, CD_3OD) δ 5.94 (s, 2H), 7.79 (dd, *J*= 0.9, 8.5Hz, 1H), 7.88 (d, *J*= 0.9Hz, 1H), 8.20 (d, *J*= 8.5Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, CD_3OD): δ 80.5 (CH_2), 123.7 (C), 124.4 (CH), 127.8 (CH), 131.8 (CH), 144.7 (C), 150.7 (C), 177.6 (C) ppm.
IR (HATR): 2801, 1671, 1643, 1613, 1586, 1545, 1464, 1447, 1417, 1310, 1290, 1212, 1173, 1119, 1082, 1067, 943, 894, 864, 855, 834, 790, 774, 752, 660 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 169 (M^+, 16), 167 (M^+, 48), 140 (33), 138 (100), 132 (20), 111 (20), 102 (44), 89 (21), 75 (60), 63 (36), 50 (86), 43 (21).
ES-MS: 168 $[M\text{-}Cl^-]^+$.
Melting Point (°C) : decomposition.
HRMS (EI): calcd for $C_8H_6NO^{35}Cl$: 167.0138; found 167.0143.

6.3.14.3 Synthesis of 7-bromo-1,3-dihydro-iminoisobenzofuran hydrochloride (4.49c).

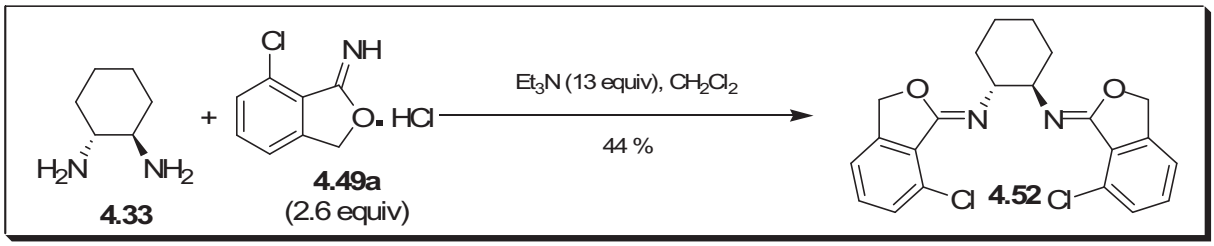


The reaction was performed on 2-bromo-6-formylbenzonitrile (**4.48c**) (500.0 mg, 2.4 mmol) according to the typical procedure resulting in 403.1 g (69 %) of imidate ester hydrochloride (**4.49c**).

Formula: $C_8H_7BrClNO$ (248,50 g/mol).
R_f (CH_2Cl_2/MeOH 90/10): 0.73
^{1}H-NMR (300 MHz, DMSO-*d*6): δ 5.90 (s, 2H), 7.84-7.88 (m, 2H), 7.94-7.99 (m, 1H) ppm.

^{13}C-NMR (75.4 MHz, DMSO-*d*6): δ 77.6 (CH_2), 118.6 (C), 122.3 (CH), 122.6 (C), 133.8 (CH), 137.8 (CH), 150.6 (C), 174.3 (C) ppm.
IR (HATR): 3328, 3154, 2670, 1682, 1602, 1577, 1514, 1467, 1444, 1404, 1319, 1295, 1226, 1191, 1150, 1124, 1058, 1046, 934, 895, 794, 745, 724, 660 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 213 ($[M-Cl]^+$, 71), 211 ($[M-Cl]^+$, 66), 184 (98), 182 (100), 157 (13), 132 (9), 102 (60), 89 (36), 75 (67), 63 (52), 51 (55).
Melting Point (℃) : decomposition.
HRMS (EI): calcd for $C_8H_7{}^{79}Br^{35}ClNO$: 246.9400; found 246.9386.

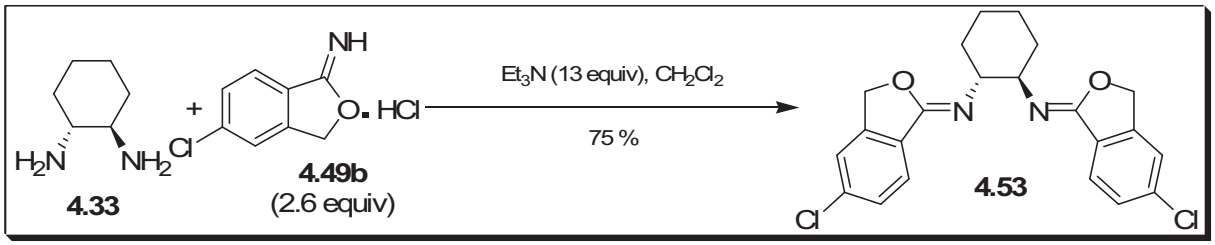
6.3.15 Synthesis of N,N'-bis-(7-chloro-3*H*-isobenzofuran-1-ylidene)-cyclohexane-(1*R*, 2*R*)-diamine (4.52)



A suspension of (1*R*, 2*R*)-(-)-diaminocyclohexane **4.33** (71.5 mg, 0.63 mmol) and imidate **4.49a** (325 mg, 1.59 mmol) in dry CH2Cl2 (3 mL) was cooled in an ice bath. Et3N (1.1 mL, 7.97 mmol) was added and the resulting suspension was refluxed for 24h. The reaction mixture was passed through a short pad of silica gel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silica gel (toluene/Et2O, 6/4, + 1% Et3N) resulted in (**4.52**) as a white solid, 114 mg (44 %).

Formula: $C_{22}H_{20}Cl_2N_2O_2$ (415.31 g/mol).
R_f (CH_2Cl_2/MeOH 90/10): 0.61
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.47-1.71 (m, 4H), 1.79-1.85 (m, 2H), 1.98-2.02 (m, 2H), 4.04 (dd, *J*= 3.7, 4.9 Hz, 2H), 5.21 (s, 4H), 7.15-7.17 (m, 2H), 7.29-7.30 (m, 4H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 24.6 (CH2), 31.9 (CH2), 61.4 (CH), 70.4 (CH2), 119.6 (CH), 127.3 (C), 129.9 (CH), 130.9 (C), 131.1 (C), 145.9 (C), 155.7 (C) ppm.
IR (HATR): 2928, 2871, 2855, 1681, 1606, 1585, 1462, 1361, 1307, 1244, 1221, 1176, 1145, 1092, 1021, 913, 772, 729, 661 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 414 (M+, 15), 379 (13), 247 (15), 206 (13), 168 (51), 152 (86), 126 (28), 124 (64), 89 (100).
Melting Point (℃) : 62℃.
Optical rotation: $[\alpha]_D^{20} = -26.1$ (*c* 0.95, $CHCl_3$).

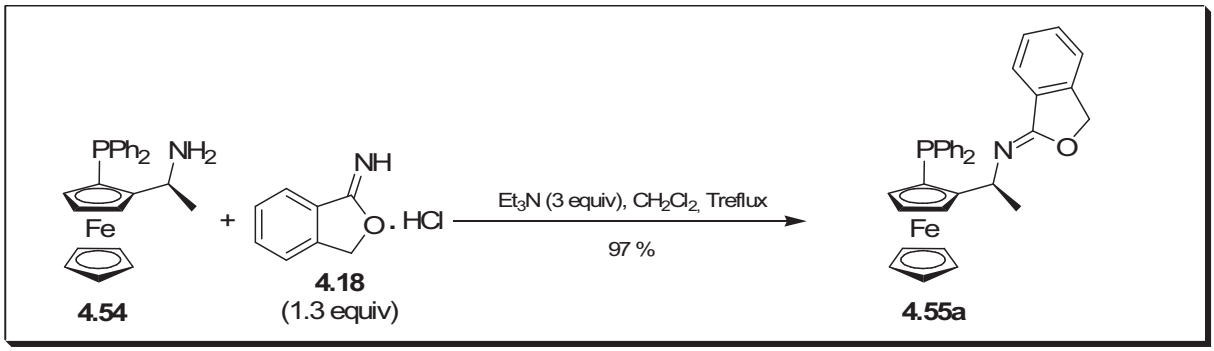
6.3.16 Synthesis of N,N'-bis-(5-chloro-3*H*-isobenzofuran-1-ylidene)-cyclohexane-(1*R*, 2*R*)-diamine (4.53)



A suspension of (1*R*, 2*R*)-(-)-diaminocyclohexane **4.33** (70.0 mg, 0.61 mmol) and imidate **4.49b** (325 mg, 1.59 mmol) in dry CH2Cl2 (3 mL) was cooled in an ice bath. Et3N (1.1 mL, 7.97 mmol) was added and the resulting suspension was refluxed for 24h. The reaction mixture was passed through a short pad of silica gel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silica gel (toluene/Et2O, 6/4, + 1% Et3N) resulted in (**4.52**) as a white solid, 190.8 mg (75 %).

Formula: $C_{22}H_{20}Cl_2N_2O_2$ (415.31 g/mol).
R_f (hexane/EtOAc 2/1): 0.21
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40-1.47 (m, 2H), 1.50-1.61 (m, 2H), 1.77-1.80 (m, 2H), 1.87-1.91 (m, 2H), 3.91 (dd, *J*= 3.7, 5.1Hz, 2H), 5.12 (d, *J*= 14.5Hz, 2H), 5.20 (d, *J*= 14.5Hz, 2H), 7.22-7.24 (m, 2H), 7.26-7.27 (m, 2H), 7.28-7.29 (m, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 24.8 (CH2), 32.3 (CH2), 61.1 (CH), 71.0 (CH2), 121.5 (CH), 124.4 (CH), 128.6 (CH), 129.4 (C), 136.8 (C), 144.6 (C), 157.6 (C) ppm.
IR (HATR): 2936, 2876, 1690, 1611, 1469, 1453, 1423, 1350, 1334, 1304, 1281, 1260, 1220, 1190, 1158, 1088, 1058, 1026, 1007, 978, 886, 867, 838, 781, 740, 713, 700, 671, 659 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 414 (M+, 16), 247 (17), 234 (7), 206 (14), 194 (24), 168 (36), 152 (74), 124 (62), 89 (100).
Melting Point (℃) : 212℃.
Optical rotation: $[\alpha]_D^{20}$ = + 60.1 (*c* 1.08, $CHCl_3$).

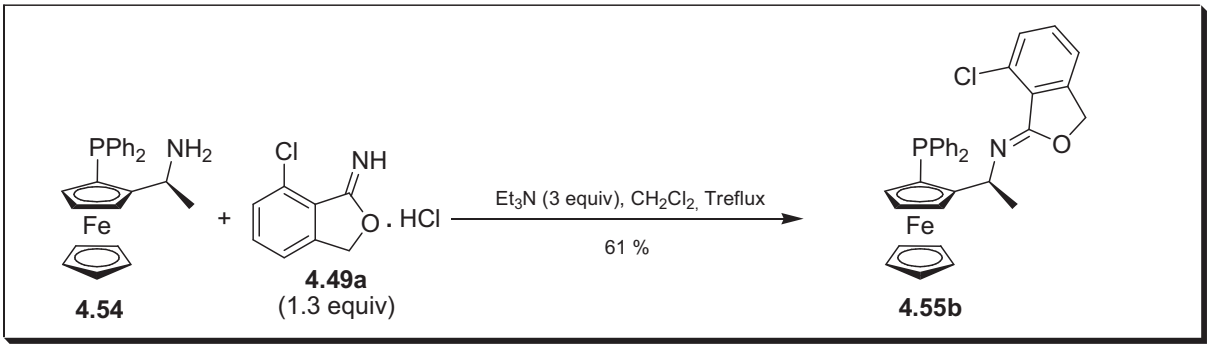
6.3.17 Synthesis of (R_p)-1-[(1*S*)-(1-(3*H*-isobenzofuran-1-ylideneamino)-ethyl)]-2-(diphenylphosphino) ferrocene (4.55a)



A suspension of (R_p)-1-[(1*S*)-(1-aminoethyl)]-2-(diphenylphosphino) ferrocene **4.54** (70.0 mg, 0.17 mmol) and imidate **4.18** (44 mg, 0.26 mmol) in dry CH_2Cl_2 (2 mL) was cooled in an ice bath. Et_3N (80.0 µL, 0.57 mmol) was added and the resulting suspension was refluxed for 48h. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 7/3) resulted in **4.55a** as a brownish oil, 87.0 mg (97 %).

Formula: $C_{32}H_{28}FeNOP$ (529.39 g/mol).
R_f (hexane/EtOAc 70/30): 0.20
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.62 (d, *J*= 6.6 Hz, 3H), 3.62-3.65 (m, 1H), 4.08 (s, 5H), 4.26-4.28 (m, 1H), 4.65 (m, 1H), 4.83 (d, *J*= 14.2Hz, 1H), 5.10 (d, *J*= 14.2Hz, 1H), 5.36-5.43 (m, 1H), 6.59-6.64 (m, 1H), 6.72-6.77 (m, 2H), 6.97-7.02 (m, 2H), 7.06-7.16 (m, 2H), 7.27-7.33 (m, 5H), 7.45-7.51 (m, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 20.7 (CH_3), 49.6 (d, J_{CP}= 8.8Hz, CH)), 68.7 (d, J_{CP}= 4.0Hz, CH), 68.8 (CH), 69.5 (5xCH), 71.3 (d, J_{CP}= 4.5Hz, CH), 71.8 (CH_2), 75.3 (d, J_{CP}= 6.6Hz, C), 98.3 (d, J_{CP}= 23.9Hz, C), 120.5 (CH), 123.6 (CH), 126.8 (CH), 127.0 (d, J_{CP}= 6.3Hz, CH), 127.4 (CH), 127.9 (d, J_{CP}= 7.7Hz, CH), 128.8 (CH), 129.8 (C), 130.4 (CH), 132.0 (d, J_{CP}= 18.6Hz, CH), 135.2 (d, J_{CP}= 20.9Hz, CH), 137.6 (d, J_{CP}= 8.6Hz, C), 139.2 (d, J_{CP}= 9.4Hz, C), 142.8 (C), 158.0 (C) ppm.
^{31}P-NMR (121.4 MHz, $CDCl_3$): - 22.5 ppm.
IR (HATR): 3050, 2972, 2931, 2873, 1681, 1469, 1451, 1433, 1363, 1290, 1243, 1167, 1106, 1081, 1044, 1017, 1000, 819, 747, 728, 697 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 529 (M^+, 8), 396 (19), 275 (8), 212 (9), 183 (17), 165 (15), 133 (11), 121 (100), 77 (17), 56 (30).
ES-MS: 530 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20} =$ - 338.8 (*c* 0.64, $CHCl_3$).
HRMS (EI): calcd for $C_{32}H_{28}FeNOP$: 529.1258; found 529.1257.

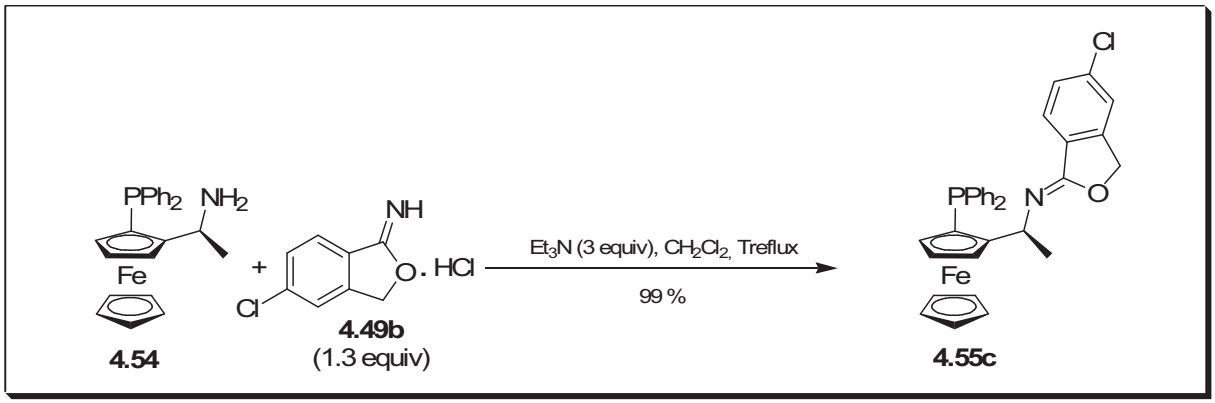
6.3.18 Synthesis of (R_p)-1-[(1*S*)-(1-(7-chloro-3*H*-isobenzofuran-1-ylideneamino)-ethyl)]-2-(diphenyl phosphino)ferrocene (4.55b)



A suspension of (R_p)-1-[(1*S*)-(1-aminoethyl)]-2-(diphenylphosphino) ferrocene **4.54** (100.0 mg, 0.24 mmol) and imidate **4.49a** (64.2 mg, 0.31 mmol) in dry CH_2Cl_2 (2.5 mL) was cooled in an ice bath. Et_3N (102.0 µL, 0.73 mmol) was added and the resulting suspension was refluxed for 48h. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 85/15) resulted in **4.55b** as a brownish oil, 80.9 mg (61 %).

Formula: $C_{32}H_{27}ClFeNOP$ (563.83 g/mol).
R_f (hexane/EtOAc 80/20): 0.38
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.64 (d, *J*= 6.6Hz, 3H), 3.62 (m, 1H), 4.08 (s, 5H), 4.27 (m, 1H), 4.65 (m, 1H), 4.72 (d, *J*= 14.3Hz, 1H) 5.01 (d, *J*= 14.3Hz, 1H), 5.33-5.41 (m, 1H), 6.54-6.59 (m, 1H), 6.75-6.80 (m, 2H), 6.93-7.02 (m, 3H), 7.14-7.21 (m, 2H), 7.30-7.35 (m, 3H), 7.45-7.52 (m, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 21.1 (CH_3), 50.0 (d, J_{CP}= 8.8Hz, CH), 68.8 (d, J_{CP}= 3.9Hz, CH), 68.9 (CH), 69.5 (5 x CH), 70.4 (CH_2), 71.0 (d, J_{CP}= 4.3Hz, CH), 75.1 (d, J_{CP}= 6.1Hz, C), 99.0 (d, J_{CP}= 24.2Hz, C), 118.9 (CH), 126.6 (CH), 126.7 (C), 127.0 (d, J_{CP}= 6.1Hz, CH), 127.9 (d, J_{CP}= 7.7Hz, CH), 128.8 (CH), 129.5 (CH), 130.8 (CH), 131.2 (C), 131.9 (d, J_{CP}= 18.3Hz, CH), 135.3 (d, J_{CP}= 21.0Hz, CH), 137.7 (d, J_{CP}= 8.8Hz, C), 139.2 (d, J_{CP}= 9.9Hz, C), 145.6 (C), 154.5 (C) ppm.
^{31}P-NMR (121.4 MHz, $CDCl_3$): - 22.0 ppm.
IR (HATR): 3054, 2972, 2931, 1678, 1606, 1585, 1478, 1462, 1433, 1361, 1306, 1265, 1244, 1220, 1167, 1106, 1078, 1040, 1026, 1000, 915, 818, 774, 738, 698, 668 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 563 (M^+, 7), 396 (100), 331 (21), 288 (21), 252 (17), 226 (6), 183 (20), 167 (32), 138 (60), 102 (31), 75 (24), 56 (52).
ES-MS: 564 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 367.6° (*c* 0.70, $CHCl_3$).
HRMS (EI): calcd for $C_{32}H_{27}NOP^{35}ClFe$: 563.0868; found 563.0857.

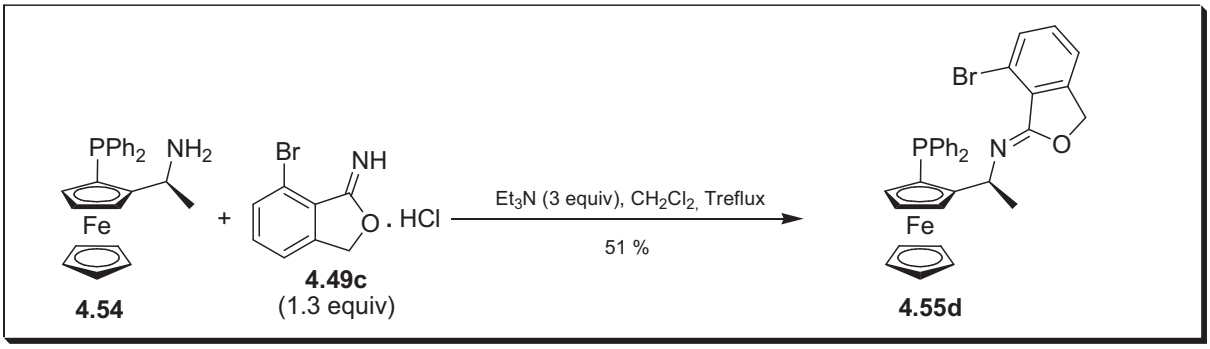
6.3.19 Synthesis of (R_p)-1-[(1*S*)-(1-(5-chloro-3*H*-isobenzofuran-1-ylideneamino)-ethyl)]-2-(diphenyl phosphino)ferrocene (4.55c)



A suspension of (R_p)-1-[(1*S*)-(1-aminoethyl)]-2-(diphenylphosphino) ferrocene **4.54** (200.0 mg, 0.48 mmol) and imidate **4.49b** (128.4 mg, 0.63 mmol) in dry CH_2Cl_2 (2.5 mL) was cooled in an ice bath. Et_3N (102.0 µL, 0.73 mmol) was added and the resulting suspension was refluxed for 48h. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 85/15) resulted in **4.55c** as a brownish oil, 266.2 mg (99 %).

Formula: $C_{32}H_{27}ClFeNOP$ (563.83 g/mol).
R_f (hexane/EtOAc 80/20): 0.22
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.63 (d, *J*= 6.6Hz, 3H), 3.66 (m, 1H), 4.11 (s, 5H), 4.30 (s, 1H), 4.67 (m, 1H), 4.83 (d, *J*= 14.4Hz, 1H) 5.09 (d, *J*= 14.4Hz, 1H), 5.37-5.44 (m, 1H), 6.70-6.75 (m, 1H), 6.80-6.84 (m, 2H), 6.99-7.04 (m, 2H), 7.09-7.28 (m, 3H), 7.34-7.35 (m, 3H), 7.47-7.53 (m, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 20.5 (CH_3), 49.8 (d, J_{CP}= 8.8Hz, CH), 68.7 (d, J_{CP}= 4.0Hz, CH), 68.9 (CH), 69.5 (5 x CH), 71.1 (CH_2), 71.4 (d, J_{CP}= 4.4Hz, CH), 75.3 (d, J_{CP}= 6.6Hz, C), 98.2 (d, J_{CP}= 23.7Hz, C), 120.9 (CH), 124.7 (CH), 126.9 (CH), 127.1 (d, J_{CP}= 6.2Hz, CH), 127.9 (d, J_{CP}= 7.7Hz, CH), 128.03 (CH), 128.7 (C), 128.8 (CH), 132.0 (d, J_{CP}= 18.6Hz, CH), 135.2 (d, J_{CP}= 20.9Hz, CH), 136.5 (C), 137.5 (d, J_{CP}= 8.7Hz, C), 139.3 (d, J_{CP}= 9.8Hz, C), 144.4 (C), 156.5 (C).
^{31}P-NMR (121.4 MHz, $CDCl_3$): - 22.6 ppm.
IR (HATR): 3067, 2969, 2931, 2871, 2358, 2341, 1689, 1613, 1473, 1456, 1432, 1354, 1304, 1265, 1242, 1222, 1192, 1167, 1106, 1080, 1042, 1018, 879, 822, 742, 697, 668 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 563 (M^+, 5), 396 (100), 331 (20), 288 (20), 252 (15), 226 (6), 183 (18), 167 (39), 138 (68), 102 (27), 75 (24), 56 (45).
ES-MS: 564 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20} = -338.1$ (*c* 0.64, $CHCl_3$).
HRMS (EI): calcd for $C_{32}H_{27}NOP^{35}ClFe$: 563.0868; found 563.0888.

6.3.20 Synthesis of (R_p)-1-[(1*S*)-(1-(7-bromo-3*H*-isobenzofuran-1-ylideneamino)-ethyl)]-2-(diphenyl phosphino)ferrocene (4.55d)



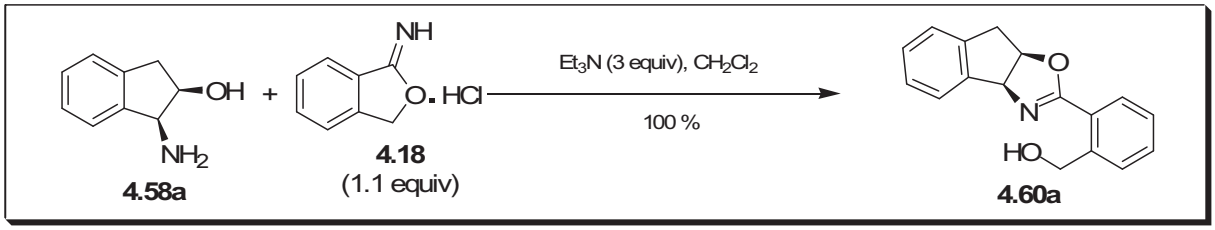
A suspension of (R_p)-1-[(1*S*)-(1-aminoethyl)]-2-(diphenylphosphino) ferrocene **4.54** (98.0 mg, 0.24 mmol) and imidate **4.49c** (77.0 mg, 0.31 mmol) in dry CH_2Cl_2 (2.5 mL) was cooled in an ice bath. Et_3N (102.0 µL, 0.73 mmol) was added and the resulting suspension was refluxed for 48h. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 85/15) resulted in **4.55c** as a brownish oil, 74.5 mg (51 %).

Formula: $C_{32}H_{27}BrFeNOP$ (608.29 g/mol).
R_f (hexane/EtOAc 70/30): 0.47
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.64 (d, *J*= 6.6Hz, 3H), 3.61 (m, 1H), 4.09 (s, 5H), 4.27 (m, 1H), 4.65-4.70 (m, 2H), 4.99 (d, *J*= 14.3Hz, 1H), 5.31-5.39 (m, 1H), 6.53-6.58 (m, 1H), 6.75-6.81 (m, 2H), 6.97-7.02 (m, 3H), 7.08-7.13 (m, 1H), 7.31-7.51 (m, 6H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 21.3 (CH_3), 49.8 (d, J_{CP}= 8.7Hz, CH), 68.8 (d, J_{CP}= 4.0Hz, CH), 68.9 (CH), 69.5 (5 x CH), 70.1 (CH_2), 71.0 (d, J_{CP}= 4.4Hz, CH), 75.0 (d, J_{CP}= 6.1Hz, C), 99.1 (d, J_{CP}= 23.9Hz, C), 119.2 (C), 119.6 (CH), 126.5 (CH), 127.1 (d, J_{CP}= 6.2Hz, CH), 127.9 (d, J_{CP}= 7.7Hz, CH), 128.2 (C), 128.9 (CH), 130.9 (CH), 131.9 (d, J_{CP}= 18.3Hz, CH), 132.9 (CH), 135.3 (d, J_{CP}= 21.0Hz, CH), 137.8 (d, J_{CP}= 8.9Hz, C), 139.2 (d, J_{CP}= 10.0Hz, C), 145.7 (C), 154.4 (C) ppm.
^{31}P-NMR (121.4 MHz, $CDCl_3$): - 22.0 ppm.
IR (HATR): 3052, 2971, 2930, 1680, 1580, 1478, 1458, 1433, 1361, 1321, 1303, 1266, 1244, 1217, 1106, 1079, 1039, 1000, 892, 819, 774, 741, 696, 668 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 607 (M^+, 5), 396 (100), 331 (22), 319 (10), 288 (22), 252 (18), 211 (20), 182 (34), 165 (27), 121 (57), 102 (27), 56 (55).
ES-MS: 607.9 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 322.2° (*c* 0.99, $CHCl_3$).
HRMS (EI): calcd for $C_{32}H_{27}NOP^{79}BrFe$: 607.0363; found 607.0382.

6.4 SYNTHESIS OF CHIRAL OXAZOLINE-ALCOHOL LIGANDS

6.4.1 A typical procedure for the preparation of chiral oxazoline-alcohol ligands (4.60)

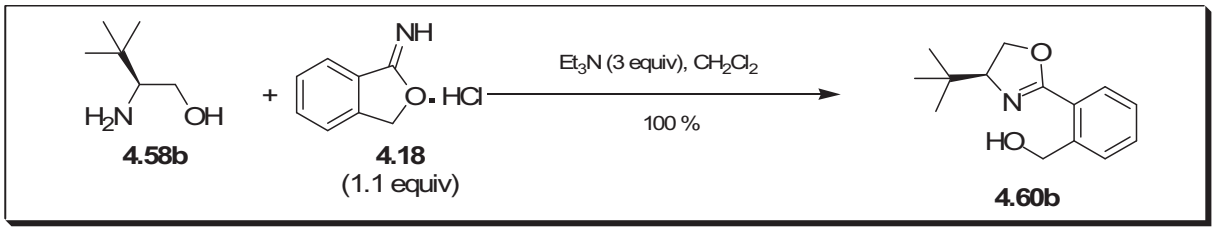
6.4.1.1 Synthesis of 2-(2'-hydroxymethyl)phenyl-(3a*S*,8a*R*)-3a,8a-dihydro-8H-indeno[1,2-*d*]oxazoline (4.60a)



A suspension of (1*S*, 2*R*)-(-)-cis-1-amino-2-indanol **4.58a** (788.0 mg, 5.28 mmol) and imidate ester **4.18** (1.0 g, 5.90 mmol) in CH_2Cl_2 (40 mL) was cooled in an ice bath. Et_3N (2.24 mL, 16.1 mmol) was added and the reaction mixture was stirred for 48h at room temperature. Evaporation in vacuo, purification by flash chromatography over silicagel (hexane/EtOAc, 2/1) and finally recrystrallization from hexane/CH_2Cl_2 resulted in **4.60a** as a white solid, 1.40 g (quant.).

Formula: $C_{17}H_{15}NO_2$ (265.31 g/mol).
R_f (hexane/EtOAc 2/1): 0.20
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.42 (d, *J*=17.8Hz, 1H), 3.56 (dd, *J*= 6.6, 17.8Hz, 1H), 4.61 (d, *J*= 5.0Hz, 1H), 4.64 (d, *J*= 5.0Hz, 1H), 5.52 (m, 1H), 5.83 (d, *J*= 7.8Hz, 1H), 6.56 (m, 1H), 7.27-7.47 (m, 6H), 7.51-7.57 (m, 1H), 7.86-7.92 (m, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 39.6 (CH_2), 64.6 (CH_2) 76.6 (CH), 83.0 (CH), 125.3 (CH), 125.4 (CH), 126.5 (C), 127.6 (CH), 127.7 (CH), 128.7 (CH), 130.2 (CH), 130.5 (CH), 131.6 (CH), 139.4 (C), 141.7 (C), 142.2 (C), 164.2 (C) ppm.
IR (HATR): 3202, 2931, 1633, 1599, 1577, 1461, 1445, 1421, 1353, 1293, 1237, 1205, 1169, 1137, 1061, 1018, 998, 968, 956, 858, 785, 778, 755, 709, 691 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 265 (M^+, 11), 133 (27), 116 (100), 115 (46), 89 (13), 77 (36), 51 (12).
ES-MS: 266 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20} = -178.5$ (*c* 1.02, $CHCl_3$).
Melting Point (℃) : 162℃.
HRMS (EI): calcd for $C_{17}H_{15}NO_2$: 265.1103; found 265.1104.

6.4.1.2 Synthesis of (*S*)-2-(2'-hydroxymethyl)phenyl-4-*tert*-butyloxazoline (4.60b)

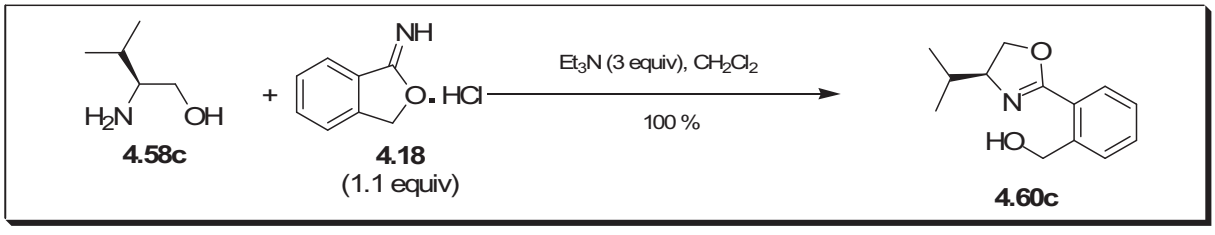


4.58b + **4.18** (1.1 equiv) → **4.60b**

The reaction was performed on (*S*)-*tert*-leucinol **4.58b** (95.0 mg, 0.81 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (CH_2Cl_2/MeOH, 98/2) resulting in pure **4.60b**, 189.0 mg (quant.).

Formula: $C_{14}H_{19}NO_2$ (233.31 g/mol).
R_f (CH_2Cl_2/MeOH 98/2): 0.46
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 4.15 (dd, *J*= 8.0, 10.1Hz, 1H), 4.25 (dd, *J*= 8.0, 8.5Hz, 1H), 4.39 (dd, *J*= 8.5, 10.1Hz, 1H), 4.60 (d, *J*= 12.3Hz, 1H), 4.73 (d, *J*= 12.3Hz, 1H), 6.82 (br s, 1H), 7.32-7.47 (m, 3H), 7.85 (m, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 25.8 (CH_3), 33.7 (C), 64.7 (CH_2), 68.4 (CH_2), 76.1 (CH), 126.6 (C), 127.6 (CH), 130.0 (CH), 130.3 (CH), 131.4 (CH), 142.2 (C), 163.7 (C) ppm.
IR (HATR): 3236, 2960, 2905, 2868, 1638, 1573, 1478, 1449, 1396, 1364, 1342, 1312, 1304, 1262, 1214, 1201, 1138, 1076, 1050, 1024, 971, 948, 785, 746, 700 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 233 (M^+, 44), 204 (12), 176 (72), 158 (50), 146 (15), 133 (100), 130 (20), 119 (32), 105 (58), 91 (36), 77 (62), 69 (26), 57 (41), 41 (80).
ES-MS: 234 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20} = -26.6$ (c 0.94, $CHCl_3$).
HRMS (EI): calcd for $C_{14}H_{19}N_2O_2$: 233.1416; found 233.1414.

6.4.1.3 Synthesis of (*S*)-2-(2'-hydroxymethyl)phenyl-4-*i*-propyloxazoline (4.60c)



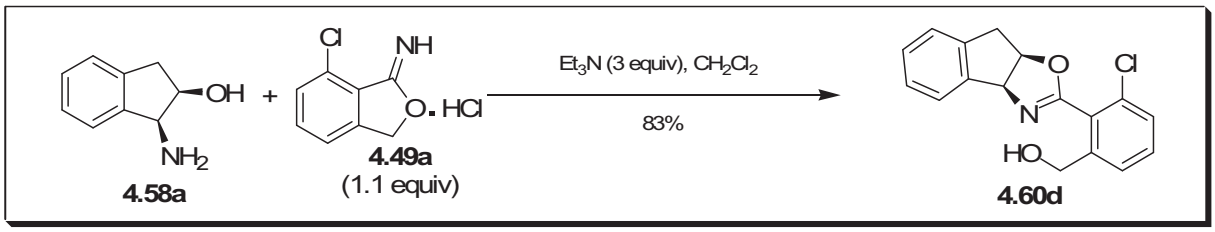
4.58c + **4.18** (1.1 equiv) → **4.60c**

The reaction was performed on (*L*)-valinol **4.48c** (116.8 mg, 1.13 mmol) according to the typical procedure. The crude product was purified by flash chromatography over silicagel (hexane/EtOAc, 70/30) resulting in pure **4.60c**, 248.0 mg (quant.).

Formula: $C_{13}H_{17}NO_2$ (219.28 g/mol).
R_f (hexane/EtOAc 70/30): 0.26

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J*= 6.7Hz, 3H), 1.03 (d, *J*= 6.7Hz, 3H), 1.83 (sept, *J*= 6.7Hz, 1H), 4.11-4.21 (m, 2H), 4.41-4.50 (m, 1H), 4.62 (dd, *J*= 6.0, 12.3Hz, 1H), 4.69 (dd, *J*= 4.8, 12.3Hz, 1H), 6.78 (dd, *J*= 4.8, 6.0Hz, 1H), 7.32-7.46 (m, 3H), 7.86 (m, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 18.6 (CH_3), 18.7 (CH_3), 33.0 (CH), 64.7 (CH_2), 70.2 (CH_2), 72.6 (CH), 126.7 (C), 127.7 (CH), 130.1 (CH), 130.4 (CH), 131.5 (CH), 142.2 (C), 163.8 (C) ppm.
IR (HATR): 3221, 2960, 2900, 2868, 1637, 1598, 1573, 1466, 1446, 1349, 1322, 1310, 1254, 1198, 1061, 1047, 1024, 963, 946, 781, 750, 711 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 219 (M^+, 40), 190 (10), 188 (6), 176 (32), 158 (21), 146 (9), 133 (100), 119 (19), 105 (54), 91 (26), 77 (47), 65 (6), 51 (16), 41 (39).
ES-MS: 220 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 42.9 (c 0.99, $CHCl_3$).
HRMS (EI): calcd for $C_{13}H_{17}NO_2$: 219.1259; found 219.1259.

6.4.1.4 2-(2'-hydroxymethyl-6'-chloro)phenyl-(3a*S*,8a*R*)-3a,8a-dihydro-8H-indeno[1,2-*d*]oxazoline (4.60d)

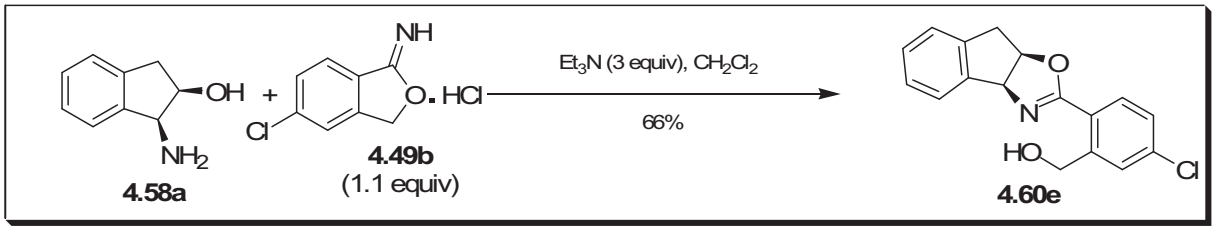


A suspension of (1*S*, 2*R*)-(-)-cis-1-amino-2-indanol **4.58a** (100.0 mg, 0.67 mmol) and imidate ester **4.49a** (150.0 mg, 0.74 mmol) in CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (0.28 mL, 2.0 mmol) was added and the reaction mixture was stirred for 48h at room temperature. Evaporation in vacuo, purification by flash chromatography over silicagel (CH_2Cl_2/MeOH, 98/2) and finally recrystallization from hexane/CH_2Cl_2 resulted in **4.60d** as a white solid, 165.1 mg (83%).

Formula: $C_{17}H_{14}ClNO_2$ (299.75 g/mol).
R_f (CH_2Cl_2/MeOH 9/1): 0.68
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.41-3.49 (dd, *J*= 1.8, 17.9Hz, 1H), 3.50-3.60 (dd, *J*= 6.1, 17.9Hz, 1H), 4.14-4.20 (dd, *J*= 6.2, 12.5Hz, 1H), 4.25-4.33 (dd, *J*= 8.1, 12.5Hz, 1H), 4.69 (dd, *J*= 6.2, 8.1Hz , 1H), 5.60 (ddd, *J*= 1.8, 6.1, 7.7Hz, 1H), 5.77 (d, *J*= 7.7 Hz, 1H), 7.23-7.37 (m, 6H), 7.52-7.57 (m, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 39.3 (CH_2), 63.5 (CH_2), 76.1 (CH), 84.2 (CH), 125.2 (CH), 125.3 (CH), 127.3 (C), 127.7 (CH), 128.7 (CH), 129.4 (CH), 131.4 (CH), 133.8 (C), 139.3 (C), 141.3 (C), 143.3 (C), 163.1 (C) ppm.
IR (HATR): 3179, 1652, 1478, 1458, 1444, 1420, 1358, 1328, 1292, 1240, 1176, 1150, 1098, 1078, 1049, 991, 853, 777, 758, 730, 714, 642 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 301 (M^+, 2), 299 (M^+, 7), 167 (12), 131 (10), 116 (100), 104 (19), 77 (32), 63 (11).
ES-MS: 300 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 209.5 (*c* 0.93, $CHCl_3$).
Melting Point (℃) : 158℃.

HRMS (EI): calcd for $C_{17}H_{14}NO_2{}^{35}Cl$: 299.0713; found 299.0719.

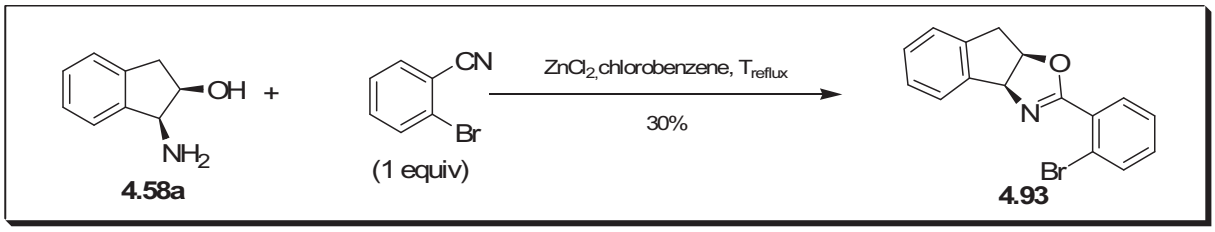
6.4.1.5 2-(2'-hydroxymethyl-4'-chloro)phenyl-(3a*S*,8a*R*)-3a,8a-dihydro-8H-indeno[1,2-*d*]oxazoline (4.60e)



A suspension of (1*S*, 2*R*)-(-)-cis-1-amino-2-indanol **4.58a** (100.0 mg, 0.67 mmol) and imidate ester **4.49b** (150.0 mg, 0.74 mmol) in CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (0.28 mL, 2.0 mmol) was added and the reaction mixture was stirred for 48h at room temperature. Evaporation in vacuo, purification by flash chromatography over silicagel (CH_2Cl_2/MeOH, 99/1) and finally recrystrallization from hexane/CH_2Cl_2 resulted in **4.60e** as white needles, 131.2 mg (66%).

Formula: $C_{17}H_{14}ClNO_2$ (299.75 g/mol).
R_f (CH_2Cl_2/MeOH 9/1): 0.80
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.38 (dd, *J*= 1.3, 17.9Hz, 1H), 3.53 (dd, *J*= 6.5, 17.9Hz, 1H), 4.53 (dd, *J*= 7.3, 12.5Hz, 1H), 4.58 (dd, *J*= 7.4, 12.5Hz, 1H), 5.49 (ddd, *J*= 1.3, 6.5, 7.9Hz, 1H), 5.79 (d, *J*= 7.9Hz, 1H), 6.47 (dd, *J*= 7.3, 7.5Hz, 1H), 7.27-7.33 (m, 5H), 7.47-7.51 (m, 1H), 7.79 (d, *J*= 8.3 Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 39.6 (CH_2), 64.2 (CH_2), 76.6 (CH), 83.1 (CH), 124.9 (C), 125.4 (2x CH), 127.7 (CH), 127.8 (CH), 128.8 (CH), 130.5 (CH), 131.6 (CH), 137.5 (C), 139.4 (C), 141.5 (C), 143.9 (C), 163.5 (C) ppm.
IR (HATR): 3340, 1621, 1595, 1564, 1482, 1456, 1444, 1428, 1400, 1348, 1306, 1292, 1278, 1246, 1229, 1199, 1142, 1103, 1040, 1031, 992, 895, 862, 824, 764, 754, 742, 712, 677 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 301 (M^+, 2), 299 (M^+, 6), 167 (8), 139 (9), 116 (100), 103 (11), 89 (8), 77 (20), 63 (4).
ES-MS: 300 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 156.4 (*c* 0.98, $CHCl_3$).
Melting Point (℃) : 147℃.
HRMS (EI): calcd for $C_{17}H_{14}NO_2{}^{35}Cl$: 299.0713; found 299.0717.

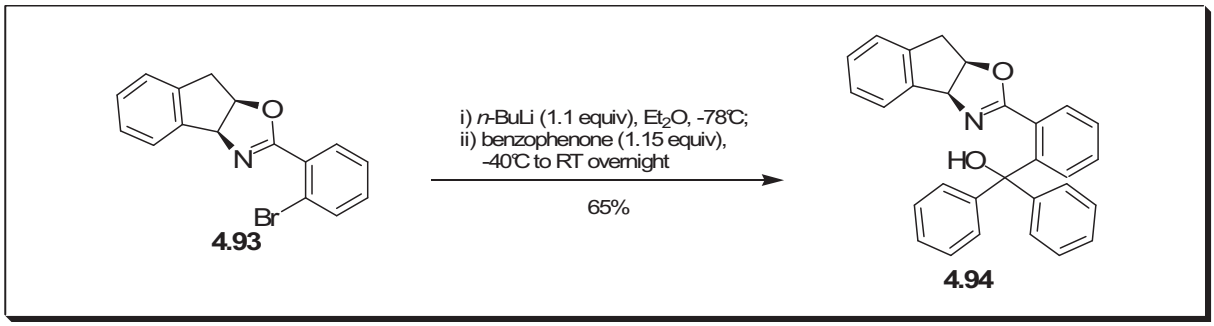
6.4.2 Synthesis of 2-(2'-bromophenyl)-(3a*S*,8a*R*)-3a,8a-dihydro-8H-indeno[1,2-*d*]oxazoline (4.93)



4.93 was synthesized according to a literature procedure.[4] A mixture of (1*S*, 2*R*)-(-)-cis-1-amino-2-indanol **4.58a** (500.0 mg, 3.35 mmol), 2-bromobenzonitrile (610.0 mg, 3.35 mmol) and anhydrous $ZnCl_2$ (23.0 mg, 0.17 mmol) in anhydrous chlorobenzene (2 mL) was refluxed for 24h. After removal of the solvent in vacuo, the crude product was purified via flash chromatography over silicagel (hexane/EtOAc, 8/2) giving **4.93** as a colourless oil, 314.2 mg (30%).

Formula: $C_{16}H_{12}BrNO$ (314.18 g/mol).
R_f (hexane/EtOAc 8/2): 0.19
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.41 (dd, *J*= 1.9, 17.9Hz, 1H), 3.51 (dd, *J*= 6.4, 17.9Hz, 1H), 5.52 (ddd, *J*= 1.9, 6.4, 8.0Hz, 1H), 5.77 (d, *J*= 8.0Hz, 1H), 7.21-7.31 (m, 5H), 7.54-7.64 (m, 3H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 39.7 (CH_2), 77.2 (CH), 83.6 (CH), 121.8 (C), 125.3 (CH), 125.7 (CH), 127.0 (CH), 127.5 (CH), 128.5 (CH), 129.8 (C), 131.5 (CH), 131.6 (CH), 133.7 (CH), 139.7 (C), 141.7 (C), 163.5 (C) ppm.
IR (HATR): 3065, 3024, 2951, 2918, 2851, 1630, 1619, 1588, 1476, 1458, 1425, 1353, 1316, 1295, 1234, 1212, 1166, 1097, 1081, 1023, 992, 749, 726, 707, 684, 676, 641 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 315 (M^+,7), 313 (M^+,7), 183 (6), 155 (4), 131 (12), 115 (26), 104 (100), 89 (14), 77 (40), 63 (14), 50 (25).
ES-MS: 314 and 316 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20}$ = - 164.7 (*c* 1.09, $CHCl_3$).
HRMS (EI): calcd for $C_{16}H_{12}NO^{79}Br$: 313.0102; found 313.0117.

6.4.3 Synthesis of 2-(2'-diphenylhydroxymethyl)phenyl-(3a*S*,8a*R*)-3a,8a-dihydro-8H-indeno[1,2-*d*]oxazoline (4.94)

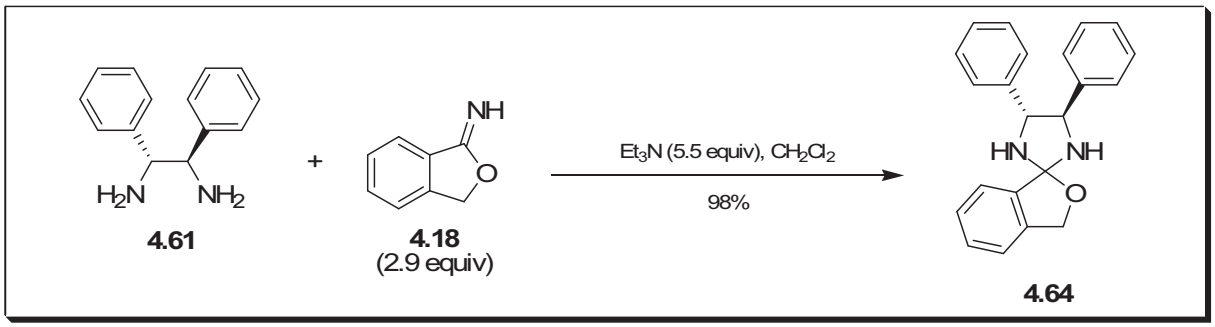


4.93 **4.94**

4.94 was synthesized according to a literature procedure.[5] A solution of **4.93** (101.7 mg, 0.33 mmol) in freshly distilled Et_2O (2.5 mL) was cooled to -78°C and treated dropwise with *n*-BuLi (0.150 mL, 0.37 mmol, 2.5 M in *n*-hexane). After being stirred for 1h at -40°C, benzophenone (71.0 mg, 0.38 mmol) was added in one portion and stirred overnight at room temperature. The reaction mixture was poured into H_2O (25 mL) and extracted with EtOAc (3 x 25 mL). The organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography over silicagel (hexane/EtOAc, 8/2) resulting in **4.94** as a white solid, 88.0 mg (65%).

Formula: $C_{29}H_{23}NO_2$ (417.50 g/mol).
R_f (hexane/EtOAc 8/2): 0.14
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.17 (d, *J*= 3.8Hz, 2H), 4.10 (br s, 1H), 4.63 (m, 1H), 5.51 (d, *J*= 4.9Hz, 1H), 6.95-7.05 (m, 2H), 7.16-7.62 (m, 15H), 7.90-7.93 (m, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 39.7 (CH_2), 63.8 (CH), 73.6 (CH), 94.2 (C), 123.8 (CH), 124.1 (CH), 125.2 (2x CH), 126.4 (CH), 126.8 (2x CH), 127.5 (CH), 127.6 (2x CH), 128.2 (CH), 128.3 (2x CH), 128.4 (3x CH), 129.0 (CH), 130.0 (C), 131.9 (CH), 141.4 (C), 141.6 (C), 142.0 (C), 142.1 (C), 148.6 (C), 159.9 (C) ppm.
IR (HATR): 3460, 3070, 3021, 2948, 2914, 1690, 1600, 1492, 1466, 1448, 1428, 1379, 1336, 1313, 1298, 1288, 1257, 1218, 1184, 1157, 1120, 1054, 1043, 984, 959, 944, 930, 866, 760, 754, 746, 718, 695, 679, 656, 632 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 417 (M^+, 4), 270 (100), 241 (36), 239 (47), 209 (21), 193 (16), 165 (51), 148 (23), 130 (66), 118 (51), 91 (50), 77 (93), 51 (41), 41 (9).
ES-MS: 418 $[M+H]^+$.
Optical rotation: $[\alpha]_D^{20} = +268.4$ (*c* 0.94, $CHCl_3$).
Melting Point (°C) : 210°C.
HRMS (EI): calcd for $C_{29}H_{23}O_2N$: 417.1729; found 417.1729.

6.5 SYNTHESIS OF CHIRAL IMIDAZOLIDINE (4.64)



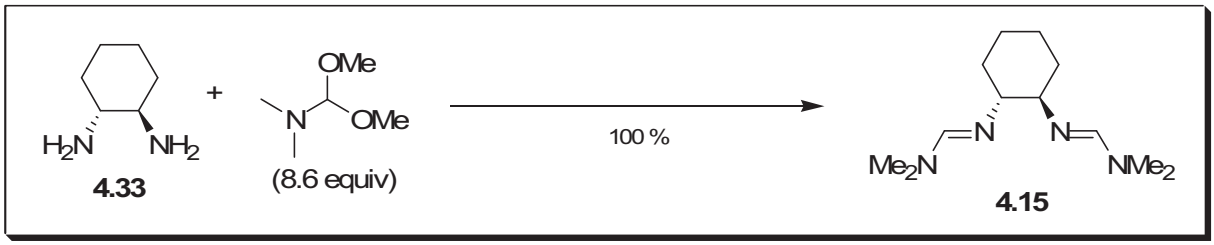
A suspension of (1*R*, 2*R*)-(+)-diphenylethylenediamine **4.61** (100 mg, 0.47 mmol) and imidate **4.18** (232 mg, 1.36 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath. Et_3N (0.36 mL, 2.6 mmol) was added and the resulting suspension was stirred at roomtemperature for 24h. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (toluene/EtOAc, 8/2, + 1% Et_3N) resulted in **4.64** as a white solid, 152.1 mg (98 %).

Formula: $C_{22}H_{20}N_2O$ (328.41 g/mol).
R_f (toluene/EtOAc, 8/2, + 1% Et_3N): 0.28
^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.55 (d, *J*= 12.1Hz, 1H), 4.75 (d, *J*= 12.1Hz, 1H), 4.90 (s, 2H), 7.20-7.44 (m, 13H), 7.68 (d, *J*= 7.5Hz, 1H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 64.7 (CH_2), 74.6 (CH), 126.5 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.9 (CH), 129.3 (C), 131.0 (CH), 131.4 (CH), 141.9 (C), 142.6 (C), 164.0 (C) ppm.
IR (HATR): 3253, 3025, 2865, 1612, 1590, 1568, 1500, 1444, 1326, 1299, 1282, 1201, 1150, 1090, 1065, 1017, 964, 920, 830, 800, 755, 698, 647 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 328 (M^+, 24), 207 (19), 180 (32), 165 (13), 149 (5), 118 (100), 84 (58), 49 (87).
ES-MS: 329 $[M+H]^+$.
Melting Point (℃) : 153℃.
Optical rotation: $[\alpha]_D^{20}$ = - 14.2 (*c* 1.0, $CHCl_3$).
HRMS (EI): calcd for $C_{22}H_{20}N_2O$: 328.1576; found 328.1559.

6.6 SYNTHESIS OF CHIRAL AMIDINE LIGANDS

4.15 and **4.90** were synthesized according to a literature procedure.[6]

6.6.1 Synthesis of [1*R*,2*R*- (1α(*E*), 2α(*E*))]-*N*,*N*'-bis(dimethylaminomethylene)-1,2-cyclohexanediamine (4.15)

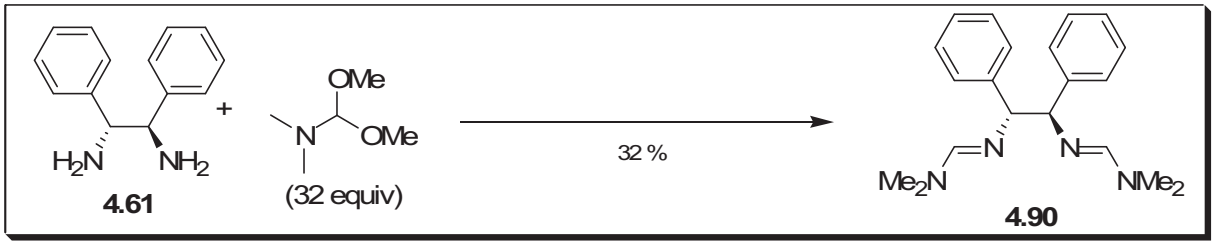


4.33 **4.15**

A mixture of (1*R*, 2*R*)-(-)-diaminocyclohexane (**4.33**) (500 mg, 4.38 mmol) and *N*,*N*-dimethylformamide dimethylacetal (5 mL, 37.6 mmol) was stirred at room temperature for 5h. The volatiles were removed in vacuo, resulting in **4.15** as a transparent oil, 0.983 g (quant.).

Formula: $C_{12}H_{24}N_4$ (224.34 g/mol).
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.20-1.74 (m, 8H), 2.71 (s, 14H), 7.14 (s, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 25.5 (CH_2), 34.9 (CH_2), 37.4 (CH_3), 70.1 (CH), 155.4 (CH) ppm.
IR (HATR): 2921, 2852, 1643, 1484, 1446, 1434, 1366, 1257, 1138, 1102, 1081, 1042, 941, 852, 844, 730 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 224 (M^+, 8), 180 (52), 154 (17), 125 (14), 111 (18), 100 (19), 98 (25), 83 (15), 72 (66), 57 (25), 44 (100).
Optical rotation: $[\alpha]_D^{20} = -192.4$ (*c* 1.0, $CHCl_3$).

6.6.2 Synthesis of [1*R*,2*R*- (1α(*E*), 2α(*E*))]-*N*,*N*'-bis(dimethylaminomethylene)-1,2-diphenylethylenediamine (4.90)



4.61 **4.90**

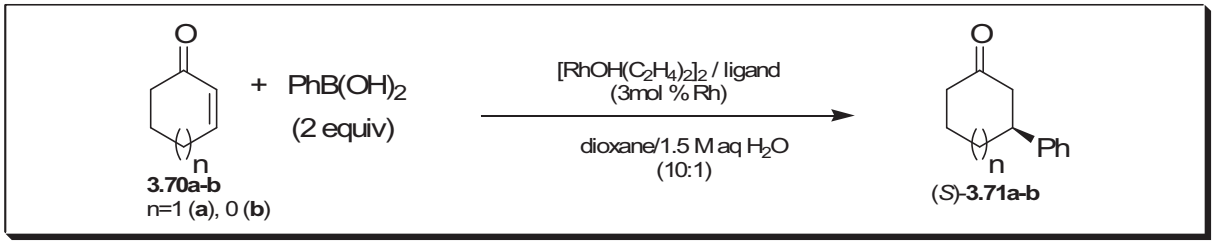
A solution of (1*R*, 2*R*)-(+)-diphenylethylenediamine **4.61** (500 mg, 2.36 mmol) and *N*,*N*-dimethylformamide dimethylacetal (10 mL, 75.2 mmol) was stirred at 50℃ for 5h. The volatiles were removed in vacuo and the solids were recrystallized from *n*-hexane/EtOAc resulting in **4.90** as a white solid, 245.1 mg (32 %).

Formula: $C_{20}H_{26}N_4$ (322.45 g/mol).

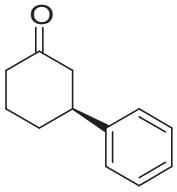
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.82 (s, 12H), 4.12 (s, 2H), 7.03-7.14 (m, 10H), 7.29 (s, 2H) ppm.
^{13}C-NMR (75.4 MHz, $CDCl_3$): 37.0 (CH_3), 77.5 (CH), 125.9 (CH), 126.5 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 144.0 (CH), 155.3 (CH) ppm.
IR (HATR): 3026, 2903, 2870, 2833, 2797, 1642, 1602, 1489, 1451, 1435, 1400, 1371, 1257, 1107, 1073, 1055, 1028, 907, 886, 844, 775, 758, 700, 628, 621 cm^{-1}.
EI-MS *m/z* (rel. intensity %): 323 (M^+, <1), 161 (100), 91 (24), 44 (42).
Optical rotation: $[\alpha]_D^{20}$ = - 132 (*c* 1.0, $CHCl_3$).

6.7 APPLICATION OF THE SYNTHESIZED LIGANDS

6.7.1 General procedure for the asymmetric 1,4-addition of phenylboronic acid to cyclic enones 3.70a and 3.70b.



(*S,S*)-nbd* (**3.10**) (2.7 mg, 9.9 µmol) and $[RhCl(C_2H_4)_2]_2$ (1.8 mg, 9.0 µmol) were dissolved in dioxane (1 mL) and stirred for 15 min at room temperature under argon. To this reaction mixture was added KOH (0.1 mL, 1.5 M, 0.15 mmol) in deoxygenated H_2O and the solution was stirred for another 15 min. Subsequently, phenylboronic acid (73.1 mg, 0.6 mmol) and 2-cyclohexenone (**3.70a**) (29 µl, 0.3 mmol) were added and stirred at 30 °C for 1.5 h. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/Et_2O, 85/15) resulted in (*S*)-**3.71a** as a colorless oil, 49.6 mg (95 %, 96% ee).

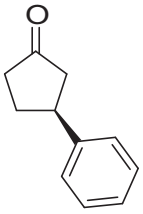


(*S*)-3.71a

Formula: $C_{12}H_{14}O$ (174.24 g/mol)
R_f (hexane/EtOAc 2/1): 0.45
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.70-1.94 (m, 2H), 2.05-2.20 (m, 2H), 2.31-2.52 (m, 2H), 2.55 (m, *J* = 13.8 Hz, 1H), 2.61 (dddd, *J* = 2.0, 2.0, 4.5, 13.8 Hz, 1H), 3.02 (dddd, *J* = 3.5, 4.5, 11.6, 11.6 Hz, 1H), 7.19-7.26 (m, 3H), 7.29-7.31 (m, 2H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 25.6 (CH_2), 32.8 (CH_2), 41.2 (CH_2), 44.8 (CH), 49.0 (CH_2), 126.6 (CH), 126.7 (CH), 128,7 (CH), 144.4 (C), 211,1 (C) ppm.
IR (KBr, film): 3061, 3028, 2938, 2865, 1712, 163, 1496, 1451, 1420, 756, 700 cm^{-1}
EI-MS *m/z* (rel. intensity %): 174 (M^+, 54), 131 (51), 117 (59), 104 (71), 84 (46), 78 (32), 65 (15), 49 (100), 42 (69).
Optical rotation: $[\alpha]_D^{20} = -20.3$ (*c* 1.0, $CHCl_3$, 96% ee).

Literature results: 1) $[\alpha]_D^{27} = -18.6$ (c 1.045, $CHCl_3$, 95% ee, *S*)[7]
2) $[\alpha]_D^{20} = -21$ (c 0.96, $CHCl_3$, 97% ee, *S*)[8]

CHIRAL HPLC: Chiralpak AS-H column, solvent: *n*-hexane/*i*-PrOH (98:2), flow rate= 1 mL/min, T= 35°C, retention times: 18.3 min for (*S*)-**3.71a**, 21.4 min for (*R*)-**3.71a**.



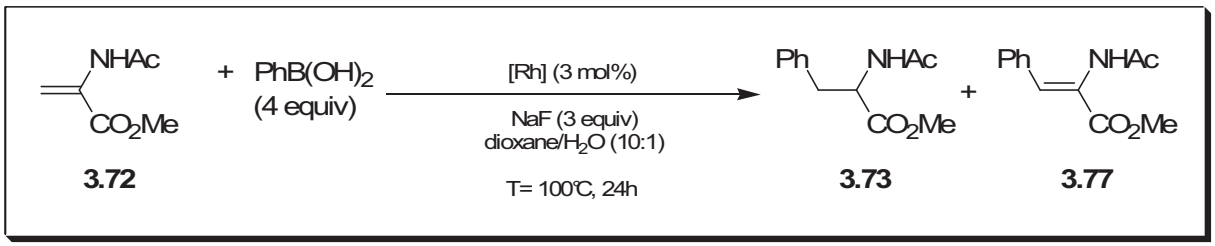
(*S*)-3.71b

Formula: $C_{11}H_{12}O$ (160.21 g/mol)
R_f (pentane/Et_2O 85/15): 0.17
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.92-2.08 (m, 1H), 2.23-2.54 (m, 4H), 2.68 (dddd, *J* = 1.6, 1.6, 7.5, 18.3 Hz, 1H), 3.43 (dddd, *J* = 6.2, 7.5, 11.3, 11.3 Hz, 1H), 7.22-7.29 (m, 3H), 7.31-7.39 (m, 2H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 31.2 (CH_2), 38.9 (CH_2), 42.2 (CH), 45.8 (CH_2), 126.7 (CH), 128.7 (CH), 143.1 (C), 218.5 (C) ppm.
IR (KBr, film): 3028, 2963, 1741, 1602, 1495, 1452, 1403,1136, 763, 700 cm^{-1}
Optical rotation: $[\alpha]_D^{20}$ = - 88.1 (*c* 1.0, $CHCl_3$, 90% ee).

Literature results: 1) $[\alpha]_D^{20}$ = - 92 (c 0.82, $CHCl_3$, 97% ee, *S*)[8]
2) $[\alpha]_D^{20}$ = + 81.2 (c 1.12, $CHCl_3$, 83% ee, *R*)[2]

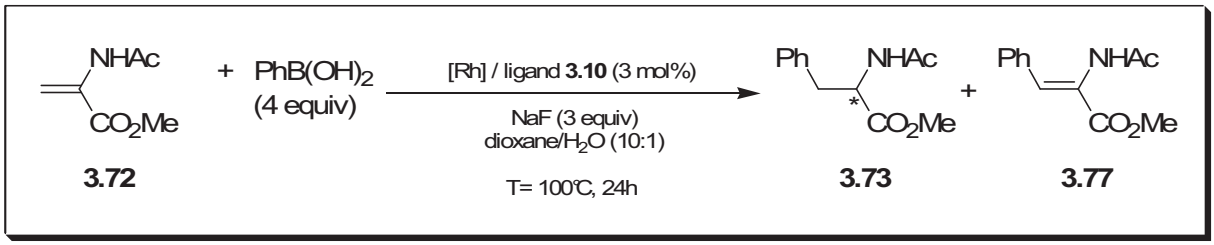
CHIRAL HPLC: Chiralpak AS-H column, solvent: *n*-hexane/*i*-PrOH (98:2), flow rate= 1 mL/min, T= 35℃, retention times: 19.9 min for (*S*)-**3.71b**, 21.7 min for (*R*)-**3.71b**.

6.7.2 General procedure for the racemic 1,4-addition of phenylboronic acid to α–acetamido acrylic ester.

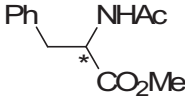


Methyl 2-acetamidoacrylate **3.72** (71.6 mg, 0.5 mmol), $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), phenylboronic acid (243.9 mg, 2 mmol) and NaF (63.0 mg, 1.5 mmol) were dissolved in dioxane (1.5 mL) and stirred for 30 min at room temperature. H_2O (150 µl) was added and the resulting reaction mixture was heated to 100℃ under argon in a sealed tube. After 26h, full conversion was observed via TLC. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/EtOAc, 50/50) resulted in a mixture of **3.73** and **3.77**, 84.5 mg (77%; 82% of **3.73** and 18% of **3.77**).

6.7.3 General procedure for the asymmetric 1,4-addition of phenylboronic acid to α–acetamido acrylic ester.

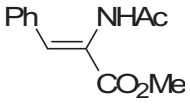


$[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 7.5 µmol) and (*S,S*)-Bn-nbd* (**3.10**) (4.5 mg, 16.5 µmol) were dissolved in degassed dioxane (0.75 mL) and degassed H_2O (75 µl) and stirred for 30 min at room temperature. After addition of methyl 2-acetamidoacrylate **3.72** (35.8 mg, 0.25 mmol), phenylboronic acid (122 mg, 1 mmol) and NaF (31.5 mg, 0.75 mmol), the resulting reaction mixture was stirred for 24h at 100°C in a sealed tube. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/EtOAc, 50/50) resulted in a mixture of **3.73** and **3.77**, 22.0 mg (40%; 30% (rac) of **3.73** and 70% of **3.77**).



3.73

Formula: $C_{12}H_{15}NO_3$ (221.25 g/mol)
R_f (hexane/EtOAc 50/50): 0.15
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.09 (dd, *J*= 5.7, 13.8, 1H), 3.16 (dd, *J*= 6.0, 13.8, 1H), 3.72 (s, 3H), 4.88 (m, 1H), 5.95 (br d, *J*= 6.4), 7.07-7.10 (m, 2H), 7.21-7.32 (m, 3H) ppm.
ES-MS: 222 $[M+H]^+$.



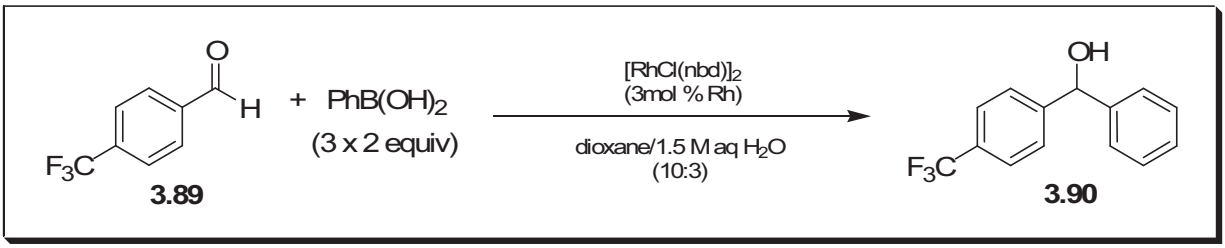
3.77

Formula: $C_{12}H_{13}NO_3$ (219.24 g/mol)
R_f (hexane/EtOAc 50/50): 0.15
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H), 3.84 (s, 3H), 7.12 (br s, 1H), 7.21-7.63 (m, 6H) ppm.
ES-MS: 220 $[M+H]^+$.

HPLC: Phenomenex Luna C18(2) column, solvent: H_2O/acetonitrile with gradient elution (0 to 100% acetonitrile in 15 min), flow rate= 1 mL/min, T= 35°C, retention times: 12.68 min for **3.77** and 12.97 min for **3.73**.

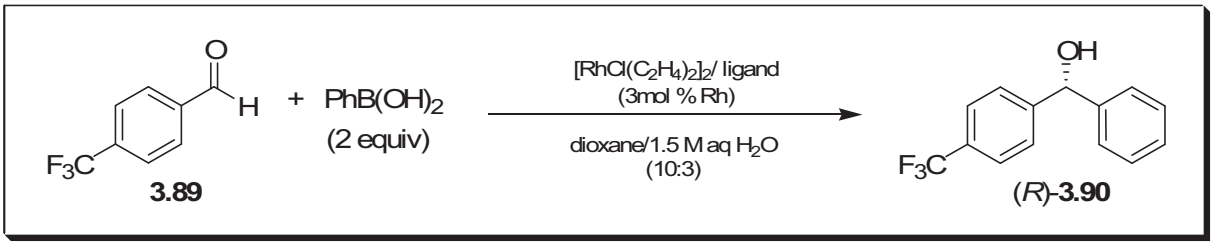
CHIRAL GC: Chirasil-Val Column (30 m x 0.25 mm x 0.25 µm); temperature program: 150℃ for 11 min, increasing to 190℃ (40° C/min); retention times: 9.11 min for *R*-**3.73**, 9.38 min for *S*-**3.73** and 14.60 min for **3.77**.

6.7.4 General procedure for the racemic 1,2-addition of phenylboronic acid to p-trifluoromethylbenzaldehyde (3.89) catalyzed by [Rh(norbornadiene)Cl]$_2$.

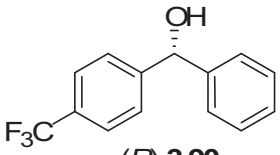


[Rh(norbornadiene)Cl]$_2$ (6.9 mg, 0.015 mmol), phenylboronic acid (121.9 mg, 1 mmol) and p-trifluoromethylbenzaldehyde (**3.89**) (68 µl, 0.5 mmol) were dissolved dioxane (1.5 mL). Aq KOH (1.5M, deoxygenated, 450 µl) was added and the resulting reaction mixture was stirred under argon at 50 ℃. After 2 h, more phenylboronic acid (121.9 mg, 1 mmol) was added, followed by another portion (121.9 mg, 1 mmol) after 4 h. After 6 h the conversion of the aldehyde was complete. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/EtOAc, 90/10) resulted in **3.90** as a white solid, 97 mg (78%).

6.7.5 General procedure for the asymmetric 1,2-addition of phenylboronic acid to p-trifluoromethylbenzaldehyde (3.89).



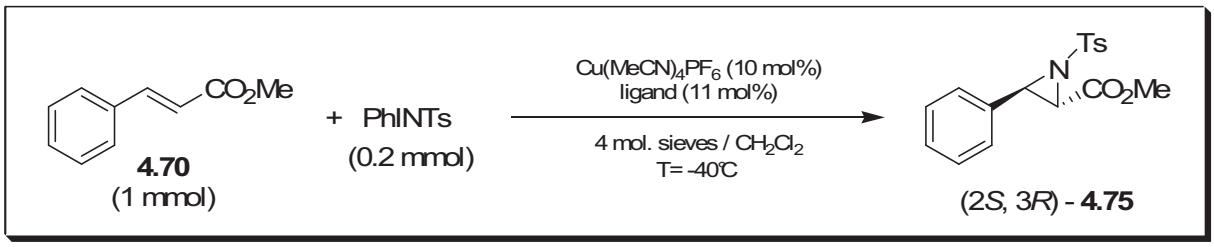
[Rh(C_2H_4)$_2$Cl]$_2$ (1.5 mg, 7.5 µmol) and (*S,S*)-i-Bu-nbd* (**3.56**) (1.6 mg, 7.8 µmol) were dissolved in dioxane (0.75 mL) and stirred for 15 min under argon. To this reaction mixture was added aqueous KOH (225 µl, 1.5 M, 0.34 mmol) in deoxygenated H_2O and the solution was stirred for another 15 min. The reaction mixture was cooled in an ice bath and phenylboronic acid (61.0 mg, 0.5 mmol) and p-trifluoromethylbenzaldehyde (**3.89**) (34 µl, 0.25 mmol) were added and stirred for 1 h. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (hexane/EtOAc, 90/10) resulted in (*R*)-**3.90** as a white solid, 62.5 mg (99 %, 37% ee).



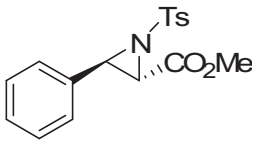
(*R*)-**3.90**

Formula: $C_{14}H_{11}F_3O$ (252.23 g/mol)
R_f (pentane/EtOAc 85/15): 0.36
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.2 (br s, 1H), 5.78 (s, 1H), 7.16-7.27 (m, 5H), 7.41 (d, *J*= 8.5 Hz, 2H), 7.49 (d, *J*= 8.5 Hz, 2H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 75.8 (CH), 125.4 (q, $J_{C\text{-}F}$= 273.0 Hz, C), 126.0 (C), 126.7 (CH), 126.7 (CH), 128.1 (CH), 128.8 (CH), 143.2 (C), 147.5 (C) ppm.
IR (KBr, film): 3346, 3065, 3032, 1620, 1495, 1454, 1326, 1165, 1124, 1067, 1016, 700, 669 cm^{-1}
EI-MS *m/z* (rel. intensiteit %): 252 (M^+, 100), 233 (20), 173 (62), 165 (21), 145 (29), 127 (32), 105 (66), 79 (47), 77 (46), 51 (33), 41 (4).
CHIRAL HPLC: Chiralcel OJ-H column, solvent: *n*-hexane/EtOH (98:2), flow rate= 1 mL/min, T= 35°C, retention times: 23.6 min for (*R*)-**3.90**, 26.5 min for (*S*)-**3.90**.

6.7.6 General procedure for the copper(I)-catalyzed asymmetric aziridination.



Bisimidate (**4.39**) (7.6 mg, 0.022 mmol) and $Cu(MeCN)_4PF_6$ (7.5 mg, 0.020 mmol) were dissolved in CH_2Cl_2 (2 mL) and stirred for 45 min at room temperature under argon. To this reaction mixture was added 4Å molecular sieves (100 mg) and methyl cinnamate **4.70** (162 mg, 1.0 mmol). The resulting suspension was cooled to -40°C. Subsequently, PhINTs (74.6 mg, 0.2 mmol) was added and stirred for 21h. The reaction mixture was passed through a short pad of silicagel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silicagel (gradient elution with hexane/EtOAc, 90/10 to hexane/EtOAc, 80/20) resulted in **4.75**, 59.3 mg (90%, 45% ee).



(2*S*, 3*R*) - **4.75**

Formula: $C_{17}H_{17}NO_4S$ (331.39 g/mol)
R_f (hexane/EtOAc 2/1): 0.30
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.51 (d, *J*= 3.9Hz, 1H), 3.84 (s, 3H), 4.42 (d, *J*= 3.9Hz, 1H), 7.21-7.32 (m, 7H), 7.77 (d, *J*= 8.3Hz, 2H) ppm.

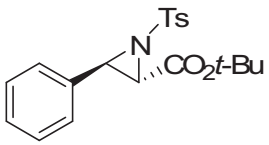
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 21.6 (CH_3), 46.8 (CH), 47.7 (CH), 53.1 (CH_3), 127.4 (CH), 127.5 (CH), 128.6 (CH), 128.9 (CH), 129.5 (CH), 132.6 (C), 137.1 (C), 144.3 (C), 166.2 (C) ppm.

Optical rotation: $[\alpha]_D^{20}$ = - 21.2 (*c* 0.78, $CHCl_3$, 51% ee).

Literature results: 1) $[\alpha]_D^{28}$ = - 18.3 (c 0.18, CH_2Cl_2, 83% ee, (2*S*,3*R*))[9]

2) $[\alpha]_D^{25}$ = + 33.1 (c 1.00, CH_2Cl_2, 94% ee, (2*R*,3*S*))[10]

CHIRAL HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (90:10), flow rate= 1 mL/min, T= 35℃, retention times: 10.7 min for (2 *R*, 3*S*)-**4.75** and 16.4 min for (2*S*, 3*R*)- **4.75**.



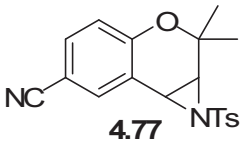
(2*S*, 3*R*) - **4.76**

Formula: $C_{20}H_{23}NO_4S$ (373.49 g/mol)

R_f (hexane/EtOAc 2/1): 0.46

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H), 2.41 (s, 3H), 3.41 (d, *J*= 4.0Hz, 1H), 4.38 (d, *J*= 4.0Hz, 1H), 7.20-7.33 (m, 7H), 7.80 (d, *J*= 8.3Hz, 2H) ppm.

CHIRAL HPLC: Chiralpak AD-H column, solvent: *n*-hexane/EtOH (90:10), flow rate= 1 mL/min, T= 35℃, retention times: 11.9 min for (2 *R*, 3*S*)-**4.76** and 13.8 min for (2*S*, 3*R*)- **4.76**.



4.77

Formula: $C_{19}H_{18}N_2O_3S$ (354.42 g/mol)

R_f (hexane/EtOAc 2/1): 0.29

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.30 (s, 3H), 2.43 (s, 3H), 3.37 (d, *J*= 7.3Hz, 1H), 3.87 (d, *J*= 7.3Hz, 1H), 6.80 (d, *J*= 8.5Hz, 1H), 7.32 (d, *J*= 8.2Hz, 2H), 7.46 (dd, *J*= 2.1, 8.5Hz, 1H), 7.55 (d, *J*= 2.1Hz, 1H), 7.81 (d, *J*= 8.2Hz, 2H) ppm.

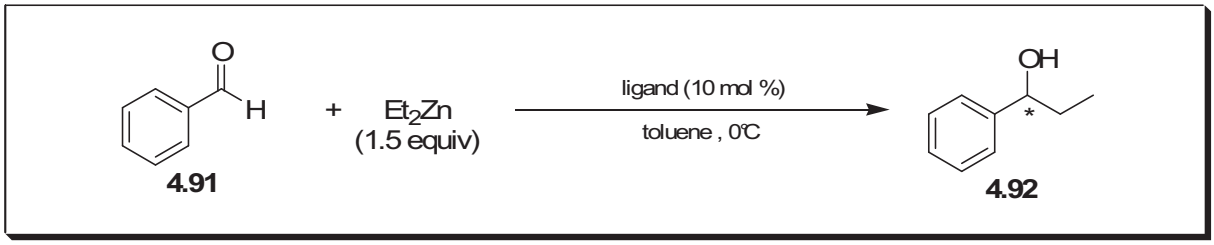
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 21.6 (CH_3), 23.8 (CH_3), 25.8 (CH_3), 38.7 (CH), 49.4 (CH), 73.2 (C), 104.7 (C), 118.5 (C), 119.3 (C), 119.3 (CH), 127.9 (CH), 129.8 (CH), 133.2 (CH), 134.2 (CH), 134.5 (C), 145.1 (C), 156.3 (C) ppm.

Optical rotation: $[\alpha]_D^{20}$ = - 14.2 (*c* 1.0, $CHCl_3$, 8% ee).

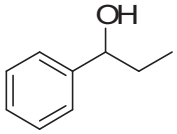
Literature results: 1) $[\alpha]_D^{25}$ = - 115.7 (c 1.65, $CHCl_3$, 70% ee, (3*S*,4*S*))[2]

CHIRAL HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (95:5), flow rate= 1 mL/min, T= 35℃, retention times: 21.8 min for (3 *S*,4*S*)-**4.77** and 24.2 min for (3*R*,4*R*)- **4.77**.

6.7.7 General procedure for the asymmetric addition of Et_2Zn to aldehyde.



Ligand (**4.60a**) (13.1 mg, 0.049 mmol) was dissolved in toluene (2 mL). Et_2Zn (0.75 mL, 0.75 mmol, 1 M in hexane) was added and the resulting yellow solution was stirred for 20 min at room temperature under argon atmosphere. Next, the reaction was cooled to 0℃ and benzaldehyde **4.91** was added (50 µL, 0.49 mmol). The reaction was stirred for another 48h. After quenching with 1 mL saturated NH_4Cl solution, the reaction was added to 25 mL H_2O and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried on Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography over silicagel (pentane/EtOAc, 90/10) resulted in **4.92**, 46.3 mg (69%, 85% ee).

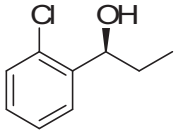


4.92

Formula: $C_9H_{12}O$ (136.19 g/mol)
R_f (pentane/EtOAc 80/20): 0.44
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82 (t, *J*= 7.4Hz, 3H), 1.56-1.82 (m, 2H), 2.09 (br s, 1H), 4.48 (t, *J*= 6.6Hz, 1H), 7.24 (s, 5H) ppm.
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 10.1 (CH_3), 31.9 (CH_2), 76.0 (CH), 126.0 (CH), 127.5 (CH), 128.4 (CH), 144.6 (C) ppm.
EI-MS *m/z* (rel. intensiteit %): 136 (M^+, 17), 107 (96), 91 (7), 79 (100), 77 (56), 51 (23).
Optical rotation: $[\alpha]_D^{20}$ = + 37.8 (*c* 1.06, $CHCl_3$, 75% ee).

Literature results: 1) $[\alpha]_D^{25}$ = + 30.2 (c 2.20, $CHCl_3$, 96% ee, *R*)[11]

CHIRAL HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (97:3), flow rate= 1 mL/min, T= 35℃, retention times: 7.8 min for (*R*)-**4.92** and 9.0 min for (*S*)- **4.92**.



(*S*)-(-)

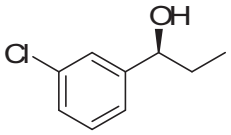
Formula: $C_9H_{11}ClO$ (170.64 g/mol)
R_f (pentane/EtOAc 90/10): 0.35
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.00 (t, *J*= 7.3Hz, 3H), 1.66-1.91 (m, 2H), 2.39 (br s, 1H), 5.07 (t, *J*= 5.8Hz, 1H), 7.17-7.35 (m, 3H), 7.52-7.56 (m, 1H) ppm.

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 10.0 (CH_3), 30.4 (CH_2), 71.9 (CH), 127.0 (CH), 127.1 (CH), 128.3 (CH), 129.3 (CH), 131.9 (C), 142.0 (C) ppm.

Optical rotation: $[\alpha]_D^{20}$ = - 30 (*c* 1.0, $CHCl_3$, 55% ee).

Literature results: 1) $[\alpha]_D^{20}$ = - 48.6 (c 1.25, C_6H_6, 85% ee, *S*)[12]

CHIRAL HPLC: Chiralcel AD-H column, solvent: *n*-hexane/EtOH (97:3), flow rate= 1 mL/min, T= 35℃, retention times: 7.7 min for (*R*) and 8.5 min for (*S*).



(*S*)-(-)

Formula: $C_9H_{11}ClO$ (170.64 g/mol)

R_f (pentane/EtOAc 80/20): 0.40

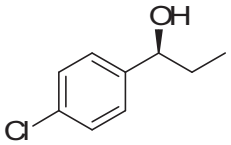
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J*= 7.4Hz, 3H), 1.70-1.87 (m, 2H), 1.96 (br s, 1H), 4.60 (t, *J*= 6.5Hz, 1H), 7.21-7.32 (m, 3H), 7.35-7.37 (m, 1H) ppm.

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.9 (CH_3), 31.9 (CH_2), 75.3 (CH), 124.1 (CH), 126.1 (CH), 127.6 (CH), 129.6 (CH), 134.3 (C), 146.6 (C) ppm.

Optical rotation: $[\alpha]_D^{20}$ = - 26.6 (*c* 1.01, $CHCl_3$, 74% ee).

Literature results: 1) $[\alpha]_D^{20}$ = - 23.3 (c 1.21, C_6H_6, 79% ee, *S*)[12]

CHIRAL HPLC: Chiralcel AD-H column, solvent: *n*-hexane/EtOH (97:3), flow rate= 1 mL/min, T= 35℃, retention times: 8.9 min for (*R*) and 10.5 min for (*S*).



(*S*)-(-)

Formula: $C_9H_{11}ClO$ (170.64 g/mol)

R_f (pentane/EtOAc 90/10): 0.22

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J*= 7.5Hz, 3H), 1.67-1.85 (m, 2H), 2.10 (br s, 1H), 4.58 (t, *J*= 6.7Hz, 1H), 7.26-7.34 (m, 4H) ppm.

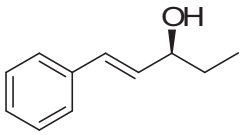
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.9 (CH_3), 31.9 (CH_2), 75.2 (CH), 127.3 (CH), 128.5 (CH), 133.0 (C), 143.0 (C) ppm.

Optical rotation: $[\alpha]_D^{20}$ = - 27.6 (*c* 1.06, $CHCl_3$, 62% ee).

Literature results: 1) $[\alpha]_D^{20}$ = - 23.3 (c 1.21, C_6H_6, 79% ee, *S*)[12]

2) $[\alpha]_D^{20}$ = - 23.5 (c 0.82, C_6H_6, 93% ee, *S*)[13]

CHIRAL HPLC: Chiralcel OB-H column, solvent: *n*-hexane/EtOH (97:3), flow rate= 1 mL/min, T= 35℃, retention times: 6.5 min for (*S*) and 7.8 min for (*R*).

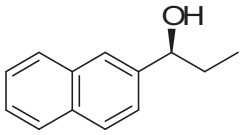


(*S*)-(-)

Formula: $C_{11}H_{14}O$ (162.23 g/mol)
R_f (pentane/EtOAc 90/10): 0.22
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.00 (t, *J*= 7.5Hz, 3H), 1.63-1.74 (m, 2H), 1.82 (br s, 1H), 4.20-4.27 (m, 1H), 6.24 (dd, *J*= 6.8, 15.9Hz, 1H), 6.60 (d, *J*= 15.9Hz), 7.24-7.43 (m, 5H) ppm.
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.7 (CH_3), 30.2 (CH_2), 74.4 (CH), 126.4 (CH), 127.6 (CH), 128.5 (CH), 130.4 (CH), 132.2 (CH), 136.7 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = - 5.5 (*c* 0.78, $CHCl_3$, 61% ee).

Literature results: 1) $[\alpha]_D^{20}$ = + 4.3 (c 2.1, $CHCl_3$, 84% ee, *R*)[12]
2) $[\alpha]_D^{24}$ = - 6.3 (c 1.73, $CHCl_3$, 88% ee, *S*)[14]

CHIRAL HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (97:3), flow rate= 1 mL/min, T= 35℃, retention times: 5.8 min for (*R*) and 7.4 min for (*S*).



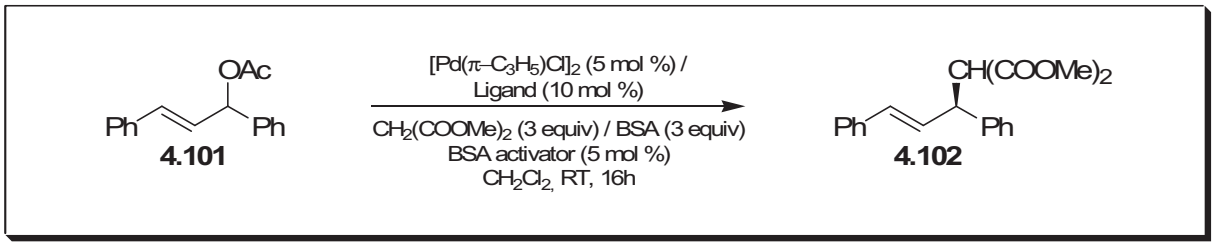
(*S*)-(-)

Formula: $C_{13}H_{14}O$ (186.10 g/mol)
R_f (pentane/EtOAc 90/10): 0.16
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J*= 7.4Hz, 3H), 1.82-1.86 (m, 3H), 4.77 (t, *J*= 6.5Hz, 1H), 7.45-7.48 (m, 3H), 7.77-7.84 (m, 4H) ppm.
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 10.1 (CH_3), 31.7 (CH_2), 76.1 (CH), 124.1 (CH), 124.7 (CH), 125.7 (CH), 126.1 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 133.0 (C), 133.3 (C), 141.9 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = - 32.2 (*c* 1.02, $CHCl_3$, 87% ee).

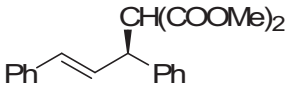
Literature results: 1) $[\alpha]_D^{20}$ = + 35.1 (c 2.4, $CHCl_3$, 92% ee, *R*)[11]

CHIRAL HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (97:3), flow rate= 1 mL/min, T= 35℃, retention times: 14.7 min for (*S*) and 16.0 min for (*R*).

6.7.8 General procedure for the palladium-catalyzed asymmetric allylic alkylation.



Imidate-phosphane ligand (**4.55b**) (12.3 mg, 21.8 µmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.0 mg, 5.5 µmol) were dissolved in degassed CH_2Cl_2 (1 mL) and stirred for 1 h at room temperature. Next, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **4.101** (55.0 mg, 0.22 mmol) in CH_2Cl_2 (0.5 mL) was added and stirred for another 30 min at room temperature. Finally, a solution of dimethylmalonate (75 µl, 0.66 mmol), BSA (160 µl, 0.66 mmol) and KOAc (1.4 mg, 10.6 µmol) in CH_2Cl_2 (0.5 mL) was added and the reaction mixture was stirred for 16h at room temperature. The reaction mixture was passed through a short pad of silica gel and eluted with CH_2Cl_2. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 90/10) resulted in *S*-**4.102**, 69.8 mg (99%, 99% ee).

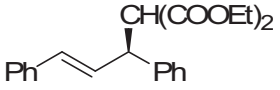


(*S*)-4.102

Formula: $C_{20}H_{20}O_4$ (324.37 g/mol)
R_f (pentane/EtOAc 9/1): 0.24
^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.72 (s, 3H), 3.99 (d, *J*= 10.8Hz, 1H), 4.30 (dd, *J*= 8.7, 10.8Hz, 1H), 6.36 (dd, *J*= 8.7, 15.7Hz, 1H), 6.51 (d, *J*= 15.7Hz, 1H), 7.20-7.36 (m, 10H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 49.3 (CH), 52.5 (CH_3), 52.7 (CH_3), 57.7 (CH), 126.5 (CH), 127.3 (CH), 127.7 (CH), 128.0 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH), 131.9 (CH), 136.9 (C), 140.3 (C), 167.9 (C), 168.3 (C) ppm.
Optical rotation: $[\alpha]_D^{20} =$ - 20.3 (*c* 0.99, $CHCl_3$, 99% ee).

Literature results: 1) $[\alpha]_D^{25}$ = - 20.6 (c 1.01, $CHCl_3$, 98% ee, *S*)[15]
2) $[\alpha]_D^{25}$ = - 22.0 (c 1.13, $CHCl_3$, 98% ee, *S*)[16]

CHIRAL HPLC: Chiralcel AD-H column, solvent: *n*-hexane/EtOH (70:30), flow rate= 1 mL/min, T= 35℃, retention times: 9.2 min for (*S*)-**4.102** and 13.9 min for (*R*)- **4.102**.

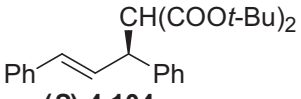


(*S*)-4.103

Formula: $C_{22}H_{24}O_4$ (352.42 g/mol)
R_f (pentane/EtOAc 9/1):0.35

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J*= 7.1Hz, 3H), 1.21 (t, *J*= 7.1Hz, 3H), 3.93 (d, *J*= 10.8Hz, 1H), 3.97 (dq, *J*= 4.7, 7.1Hz, 1H), 3.99 (dq, *J*= 4.7, 7.1Hz, 1H), 4.18 (q, *J*= 7.1Hz, 2H), 4.27 (dd, *J*= 8.7, 10.8Hz, 1H), 6.35 (dd, *J*= 8.7, 15.7Hz, 1H), 6.49 (d, *J*= 15.7Hz, 1H), 7.18-7.36 (m, 10H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 13.9 (CH_3), 14.2 (CH_3), 49.3 (CH), 57.9 (CH), 61.5 (CH_2), 61.7 (CH_3), 126.5 (CH), 127.2 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 131.4 (CH), 136.9 (C), 140.4 (C), 167.5 (C), 168.0 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = - 16.6 (*c* 0.99, $CHCl_3$, 99% ee).

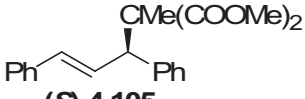
Literature results: 1) $[\alpha]_D^{25}$ = - 17.2 (c 1.02, $CHCl_3$, 97% ee, *S*)[15]
CHIRAL HPLC: Chiralcel AD-H column, solvent: *n*-hexane/EtOH (80:20), flow rate= 1 mL/min, T= 35℃, retention times: 6.9 min for (*S*)-**4.103** and 8.7 min for (*R*)- **4.103**.



(*S*)-4.104

Formula: $C_{26}H_{32}O_4$ (408.53 g/mol)
R_f (hexane/EtOAc 95/5): 0.26
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.42 (s, 9H), 3.73 (d, *J*= 10.9Hz, 1H), 4.16 (dd, *J*= 8.4, 10.9Hz, 1H), 6.34 (dd, *J*= 8.4, 15.8Hz, 1H), 6.45 (d, *J*= 15.8Hz, 1H), 7.17-7.34 (m, 10H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 27.7 (CH_3), 28.7 (CH_3), 49.2 (CH), 59.4 (CH), 81.7 (C), 81.9 (C), 126.4 (CH), 127.0 (CH), 127.5 (CH), 128.3 (CH), 128.6 (CH), 128.6 (CH), 130.3 (CH), 131.3 (CH), 137.2 (C), 140.9 (C), 166.9 (C), 167.4 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = - 12.2 (*c* 1.0, $CHCl_3$, 99% ee).

Literature results: 1) $[\alpha]_D^{25}$ = - 9.3 (c 1.01, $CHCl_3$, 80% ee, *S*)[15]
CHIRAL HPLC: Chiralcel AD-H column, solvent: *n*-hexane/EtOH (80:20), flow rate= 1 mL/min, T= 35℃, retention times: 10.6 min for (*S*)-**4.104** and 15.4 min for (*R*)- **4.104**.

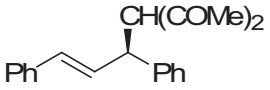


(*S*)-4.105

Formula: $C_{21}H_{22}O_4$ (338.40 g/mol)
R_f (hexane/EtOAc 90/10): 0.23
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.49 (s, 3H), 3.63 (s, 3H), 3.71 (s, 3H), 4.31 (d, *J*= 9.0Hz, 1H), 6.47 (d, *J*= 15.7Hz, 1H), 6.69 (dd, *J*= 9.0, 15.7Hz, 1H), 7.15-7.38 (m, 10H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 18.8 (CH_3), 52.6 (CH_3), 52.6 (CH_3), 54.0 (CH), 59.3 (C), 125.4 (CH), 126.5 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 128.6 (CH), 129.2 (CH), 129.6 (CH), 132.9 (CH), 137.4 (C), 139.4 (C), 171.4 (C), 171.7 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = + 61.9 (*c* 1.1, CH_2Cl_2, >99% ee).

Literature results: 1) $[\alpha]_D^{25}$ = + 60.1 (c 1.20, CH_2Cl_2, 98% ee, *S*)[16]
CHIRAL NMR: The enantiomeric excess was determined by ^{1}H NMR using $Eu(hfc)_3$ as a resolving agent. The two signals at 3.63 (s) and 3.71 (s) are splitting up in the presence of $Eu(hfc)_3$. To 11.3 mg of **4.105** in 0.7mL $CDCl_3$ was added 18.5 mg

$Eu(hfc)_3$. Integration of the signals was performed after applying a resolution enhancing Gaussian window function to the FID.

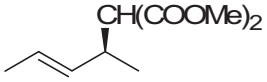


(*S*)-4.106

Formula: $C_{20}H_{20}O_2$ (292.37 g/mol)
R_f (pentane/EtOAc 90/10): 0.26
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.26 (s, 3H), 4.35 (m, 2H), 6.20 (ddd, *J*= 2.0, 6.0, 15.0Hz, 1H), 6.44 (d, *J*= 15.0Hz, 1H), 7.18-7.37 (m, 10H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 29.9 (CH_3), 30.2 (CH_3), 49.3 (CH), 74.6 (CH), 126.5 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 131.8 (CH), 136.6 (C), 140.2 (C), 202.9 (C), 203.0 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = + 6.8 (*c* 1.0, EtOH, 94% ee).

Literature results: 1) $[\alpha]_D^{23}$ = + 5.9 (c 1.30, EtOH, 93% ee, *S*)[17]

CHIRAL HPLC: Chiralcel AD-H column, solvent: *n*-hexane/EtOH (99:1), flow rate= 1 mL/min, T= 35℃, retention times: 21.1 min for (*S*)-**4.106** and 25.8 min for (*R*)- **4.106**.

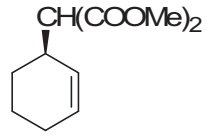


(*S*)-4.108

Formula: $C_{10}H_{16}O_4$ (200.23 g/mol)
R_f (pentane/EtOAc 9/1): 0.51
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.04 (d, *J*= 6.8Hz, 3H), 1.61 (dd, *J*= 1.5, 6.4Hz, 3H), 2.88 (m, 1H), 3.25 (d, *J*= 9.1Hz, 1H), 3.68 (s, 3H), 3.71 (s, 3H), 5.33 (ddd, *J*= 1.5, 8.3, 15.2Hz, 1H), 5.51 (dqd, *J*= 0.6, 6.4, 15.2Hz, 1H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 18.0 (CH_3), 18.6 (CH_3), 37.5 (CH), 52.3 (CH_3), 52.5 (CH_3), 58.1 (CH), 126.5 (CH), 132.4 (CH), 169.0 (2x C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = - 25.1 (*c* 1.1, $CHCl_3$, 83% ee).

Literature results: 1) $[\alpha]_D^{25}$ = - 20.9 (c 1.26, CH_2Cl_2, 65% ee, *S*)[16]

CHIRAL NMR: The enantiomeric excess was determined by ^{1}H NMR using (+)-$Eu(hfc)_3$ as a resolving agent. The signal at 1.04 (d) is splitting up in the presence of (+)-$Eu(hfc)_3$. To 11.2 mg of **4.108** in 0.7mL $CDCl_3$ was added 9.0 mg (+)-$Eu(hfc)_3$.



(*R*)-4.110

Formula: $C_{11}H_{16}O_4$ (212.25 g/mol)
R_f (pentane/EtOAc 90/10): 0.33

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.3-1.4 (m, 1H), 1.5-1.6 (m, 1H), 1.6-1.8 (m, 2H), 1.98 (m, 2H), 2.90 (m, 1H), 3.28 (d, *J*= 9.5Hz, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 5.51 (dd, *J*= 2.0, 10.2Hz, 1H) 5.74-5.80 (m, 1H) ppm.
^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 21.0 (CH_2), 25.0 (CH_2), 26.7 (CH_2), 35.5 (CH), 52.5 (CH_3), 57.0 (CH), 127.4 (CH), 129.8 (CH), 169.0 (C), 169.0 (C) ppm.
Optical rotation: $[\alpha]_D^{20}$ = + 32.1 (c 0.91, $CHCl_3$, 74% ee).

Literature results: 1) $[\alpha]_D^{25}$ = + 32.1 (c 1.0, CH_2Cl_2, 64% ee, *R*)[18]

CHIRAL NMR: The enantiomeric excess was determined by ^{1}H NMR using (+)-Eu(hfc)$_3$ as a resolving agent. The two signals at 3.71 (s) and 3.72 (s) are splitting up in the presence of (+)-Eu(hfc)$_3$. To 13.4 mg of **4.110** in 0.7mL $CDCl_3$ was added 16.6 mg (+)-Eu(hfc)$_3$. Integration of the signals was performed after applying a resolution enhancing Gaussian window function to the FID.

6.8 REFERENCES

[1] (a) Berkessel, A.; Schröder, M.; Sklorz, C.A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J.M. *J. Org. Chem.* **2004**, *69*, 3050-3056. (b) For the synthesis of (1*S*, 4*S*)-bicyclo[2.2.1]heptane-2,5-dione: Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967.

[2] Vandyck, K. In *Synthese en toepassing van rigide C_2-symmetrische bidentaat liganden,* Ph.D. thesis, Universiteit Gent, **2006**.

[3] Sun, C.; Xu, B. *J. Org. Chem.* **2008**, *73*, 7361-7364.

[4] Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467-4478.

[5] Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860-7867.

[6] Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227-4240.

[7] Defieber, C.; Paquin, J.F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873-3876.

[8] Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580.

[9] Suga, H.; Kakehi, A.; Ito, S.; Ibata, T.; Fudo, T.; Watanabe, Y.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 189-199.

[10] Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; Anderson, B.A.; Barnes, D.M. *J. Am. Chem. Soc.* **1993**, *115*, 5328-5329.

[11] Bulut, A.; Aslan, A.; Izgü, E.C.; Dogan, Ö. *Tetrahedron: Asymmetry* **2007**, *18*, 1013-1016.

[12] Bauer, T.; Gajewiak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 851-855.

[13] Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071-6072.

[14] Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979-3984.

[15] Tanaka, Y.; Mino, T.; Akita, K.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2004**, *69*, 6679-6687.

[16] Evans, D.A.; Campos, K.R.; Tedrow, J.S.; Michael, F.E.; Gagné, M.R. *J. Am. Chem. Soc.* **2000**, *122*, 7905-7920.

[17] Sun, X.-M.; Koizumi, M.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *347*, 1893-1898.

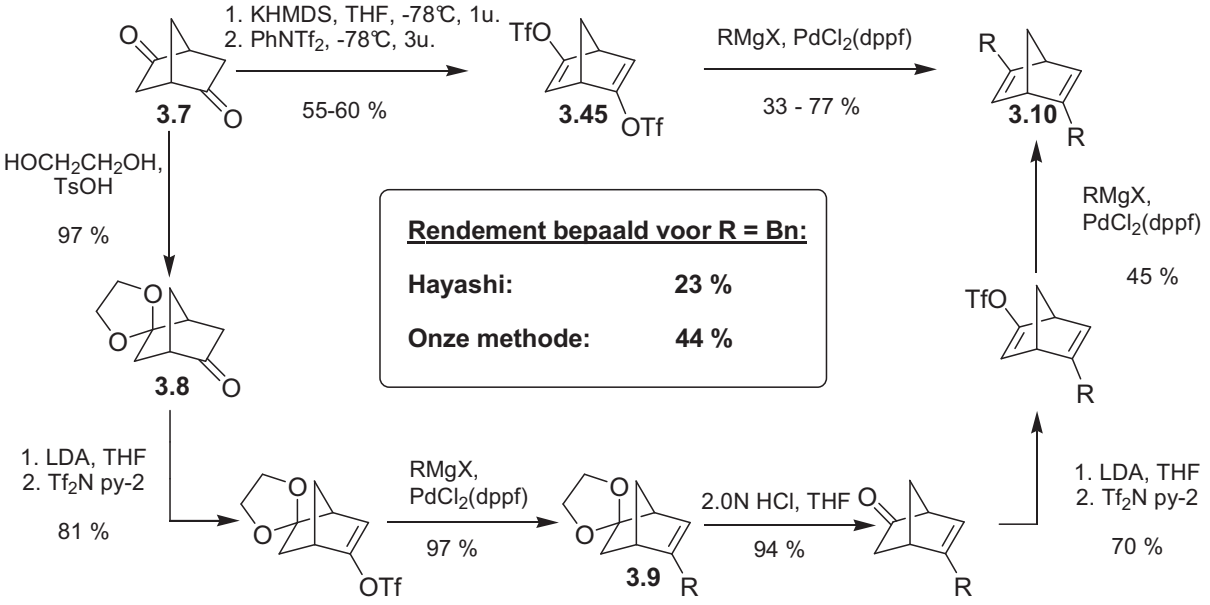
[18] Cheung, H.Y.; Yu, W.-Y.; Au-Yeung, T.T.L.; Zhou, Z.; Chan, A.S.C. *Adv. Synth. Catal.* **2009**, *351*, 1412-1422.

7

NEDERLANDSE SAMENVATTING EN TOEKOMST-PERSPECTIEVEN

In dit werk worden twee belangrijke ligandklassen bestudeerd, nl. chirale dieen liganden en chirale imidaat liganden. Gemeenschappelijk aan beiden is dat hun gebruik in de asymmetrische katalyse tot voor kort verhinderd werd door hun veronderstelde instabiliteit.

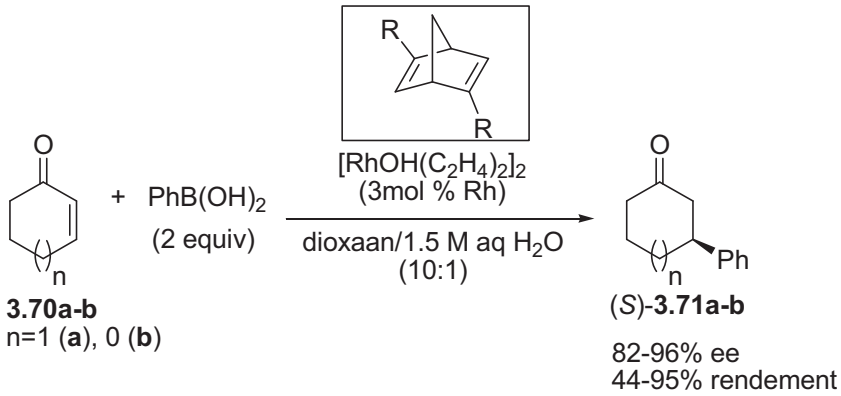
In 2003 beschreef Hayashi *et al.* voor het eerst het gebruik van chirale dieen liganden in asymmetrische katalyse. Hoewel de katalytische eigenschappen van deze liganden excellent waren, bleek dat de synthese ervan omslachtig was.[1] In hoofdstuk 3, beschrijven we de ontwikkeling van een nieuwe syntheseroute voor deze chirale digesubstitueerde bicyclo[2.2.1]heptadienen (Scheme 7.1). Voordelen van deze benadering zijn enerzijds het hogere totaalrendement en anderzijds de mogelijkheid tot simultane introductie van de zijketens.[2]



Schema 7.1. *Vergelijking van onze nieuwe methode voor de synthese van chirale bicyclo[2.2.1]heptadieen liganden met de oorspronkelijke methode van Hayashi.*

Via deze methode synthetiseerden we het Hayashi ligand met de benzyl zijketen en drie nieuwe liganden (met R= *i*-Bu, *c*-Hex and Allyl). Een NMR studie van het rhodium complex van (*S*,*S*)-allyl-nbd* toonde aan dat de coördinatie met het metaal enkel gebeurde via de norbornadieen dubbele bindingen. Dit staat in contrast met de bevindingen van Carreira.[3]

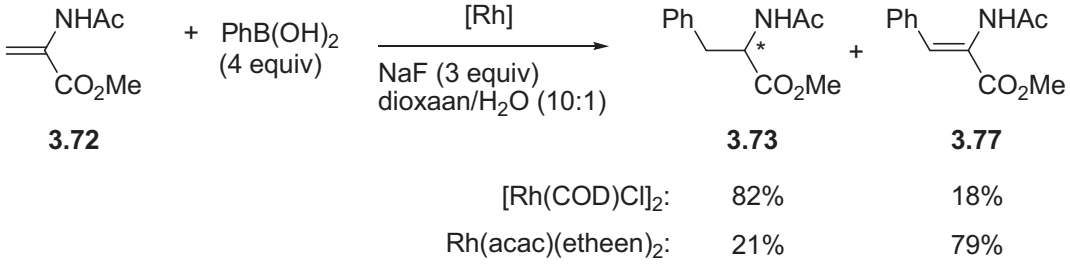
De gesynthetiseerde dieen liganden werden getest in verschillende rhodium-gekatalyseerde asymmetrische testreacties. Er werden heel goede enantioselectiviteiten (tot 96% ee) behaald in de rhodium(I)-gekatalyseerde 1,4-additie van fenylboronzuren aan cyclische enonen (schema 7.2). Een toename in sterische hinder van de ligand substituenten leidde niet tot een significant verschil in selectiviteit. De reactiesnelheid werd daarentegen wel sterk beïnvloed.



Scheme 7.2. *Rhodium(I)-gekatalyseerde asymmetrische 1,4-additie van $PhB(OH)_2$ aan cyclische enonen.*

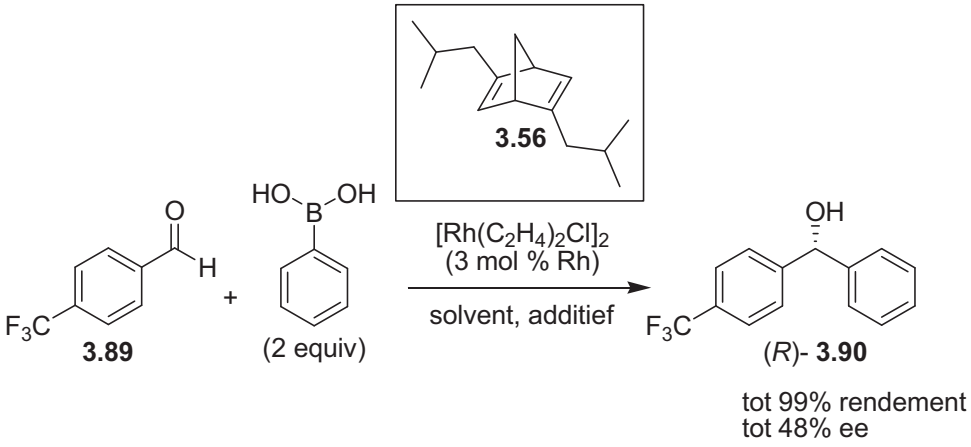
In de 1,4-additie van fenylboronzuren aan α-acetamido acrylester **3.72** werd ook de vorming van een Heck-type product **3.77** geobserveerd. Bovendien kon de

verhouding van het conjugaat adduct **3.73** en het Heck product **3.77** beïnvloed worden door een geschikte keuze van het ligand in de achiral versie (Schema 7.3). In de asymmetrische versie van dit type reactie met ligand **3.10** werden lage rendementen en enantioselectiviteiten bekomen.



Schema 7.3. *Rhodium(I)-gekatalyseerde 1,4-additie versus Heck reactie.*

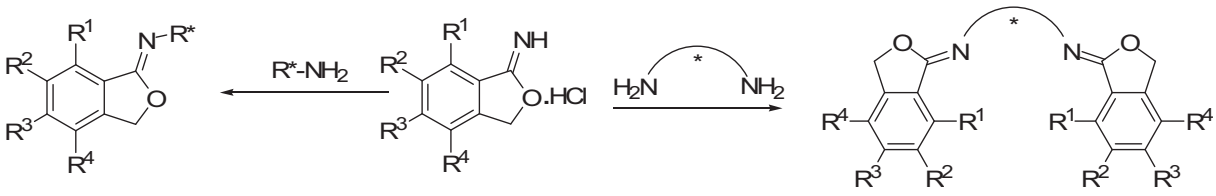
Als laatste bestudeerden we de rhodium-gekatalyseerde 1,2-additie van fenylboronzuren aan benzaldehyden. Deze reactie kan beschouwd worden als een grote uitdaging. De aanwezigheid van alkyl zijketens in het ligand bleek een cruciale rol te spelen voor de katalytische activiteit. Dit resulteerde in een sterk verhoogde reactiviteit ten opzichte van het ongesubstitueerde norbornadieen als ligand. Enantioselectiviteiten konden verhoogd worden van laag tot middelmatig met ligand **3.56** (tot 48% ee) (Schema 7.4).



Schema 7.4. *Rhodium(I)-gekatalyseerde asymmetrische 1,2-additie van $PhB(OH)_2$ aan p-trifluoromethylbenzaldehyd.*

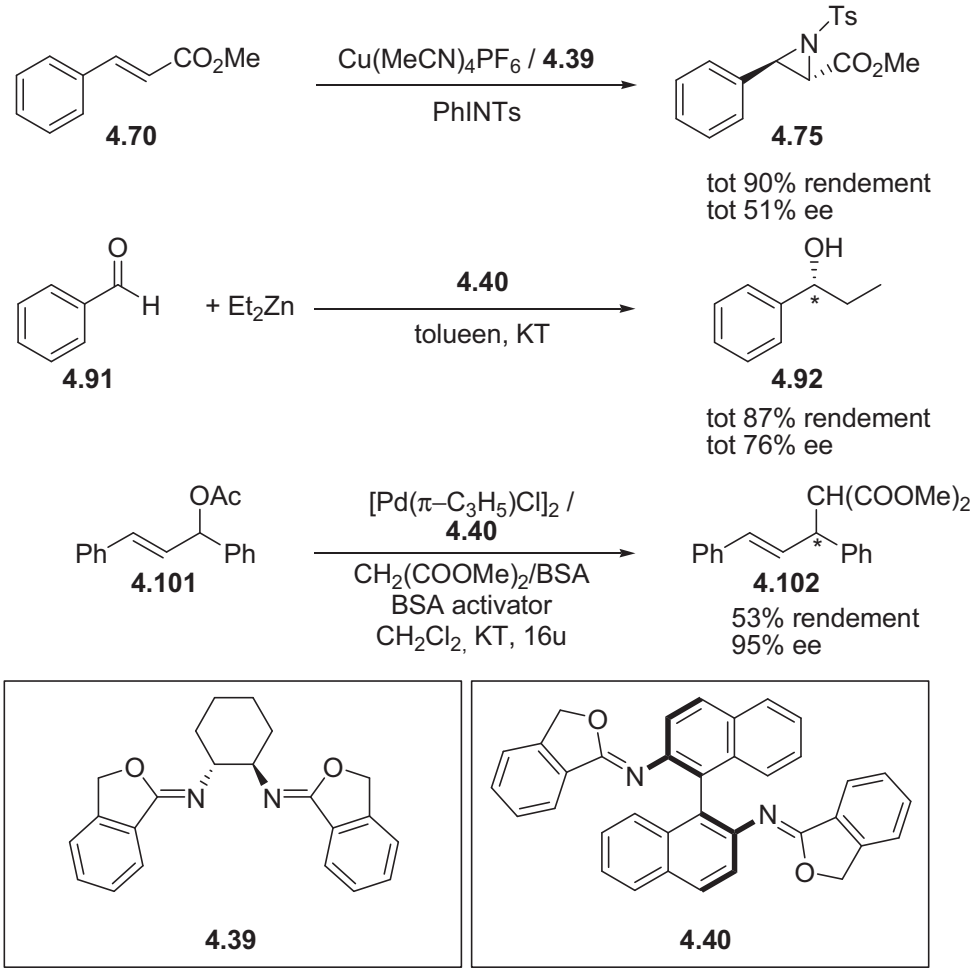
In hoofdstuk 4 beschrijven we de ontwikkeling van chirale imidaten als een nieuwe ligand familie. Imidaten werden nooit eerder als liganden beschreven in de literatuur. Dit is waarschijnlijk te wijten aan hun vermeende instabiliteit.

Een belangrijke factor die de bruikbaarheid van een ligand bepaalt voor asymmetrische synthese is het gemak waarmee het gesynthetiseerd kan worden. We hebben aangetoond dat deze imidaat liganden vlot gesynthetiseerd kunnen worden startende van een centrale precursor.[4] Bovendien kunnen deze imidaat liganden verder geoptimaliseerd worden door het plaatsen van substituenten op de aromatische ring van de imidaat ligand precursor (Schema 7.5).



Schema 7.5. *Synthese van een imidaat ligand familie.*

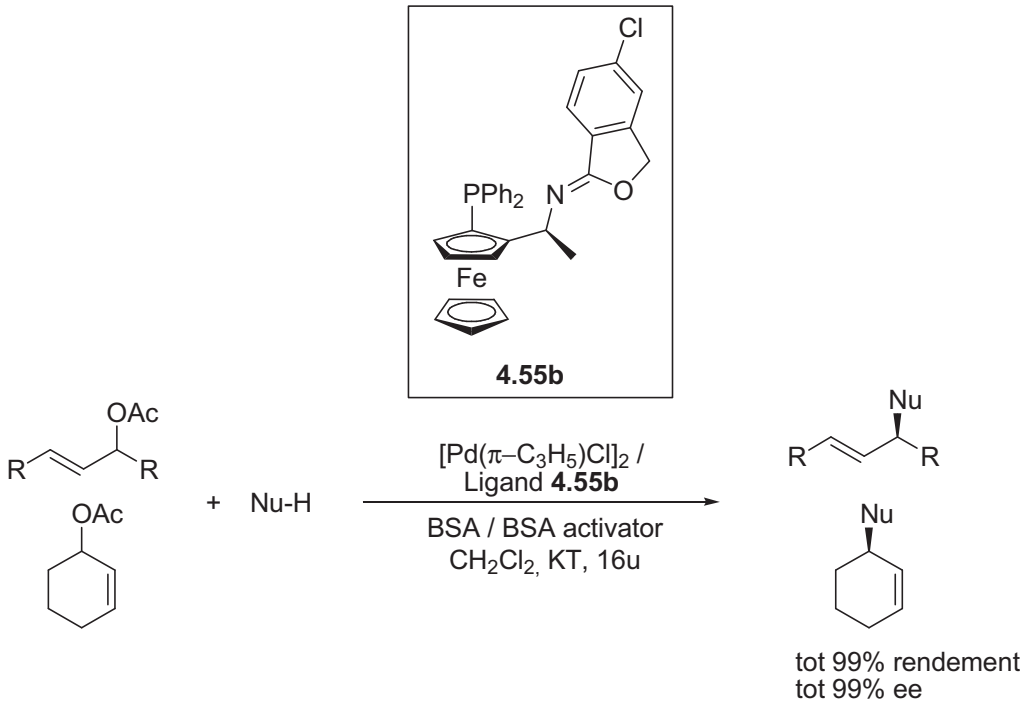
De gesynthetiseerde monodentaat en bidentaat liganden werden getest in verschillende asymmetrische testreacties (Schema 7.6**)**. In de koper(I)-gekatalyseerde asymmetrische aziridinering behaalden we meestal hoge rendementen (tot 90% rendement) en middelmatige enantioselectiviteiten (51% ee) met ligand **4.39**. De asymmetrische additie van diethylzink aan benzaldehyd resulteerde in hoge rendementen (tot 87% rendement) en goede enantioselectiviteiten (tot 76% ee) met ligand **4.40**. Het beste resultaat werd echter behaald met ligand **4.40** in de asymmetrische allylische alkylatie: een middelmatig rendement (53% rendement) maar een excellente enantioselectiviteit (95% ee).



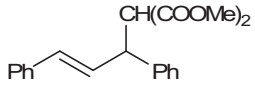
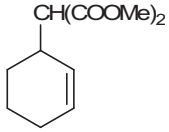
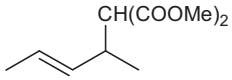
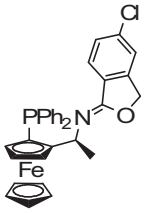
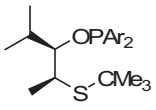
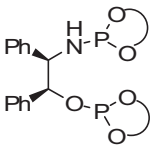
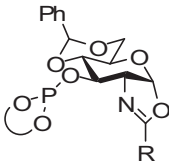
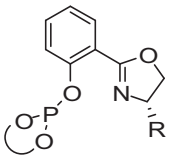
Schema 7.6. *Toepassing van bisimidaat liganden in asymmetrische aziridineringen, asymmetrische diethylzink additie en asymmetrische allylische alkyleringen.*

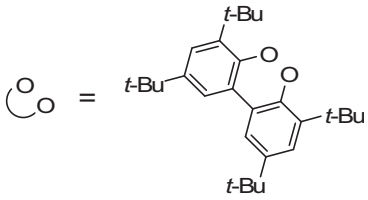
Verder hebben we ook gemengde imidaat-fosfaan liganden ontwikkeld als een nieuw type P,N liganden. Deze liganden zijn eenvoudig te synthetiseren in één stap via een

condensatie van een commercieel verkrijgbaar aminofosfaan en een imidaat ligand precursor. De liganden bleken heel waardevol te zijn in palladium-gekatalyseerde allylische substitutie reacties (Schema 7.7). Schitterende resultaten werden behaald met dit katalysator systeem in de allylische alkylering van 1,3-difenyl-2-propenyl acetaat met verschillende nucleofielen (tot 99% rendement en 99% ee). Dit katalysatorsysteem bleek ook goede resultaten te geven in de allylische alkylatie van lineaire ongehinderde en cyclische substraten. Zelden zijn enantioselectieve katalysatoren succesvol in beide substraatklassen. Om deze reden kan deze imidaat-fosfaan familie concurreren met enkele andere liganden die ook hoge selectiviteiten geven voor zowel gehinderde als ongehinderde substraten (Tabel 7.1).



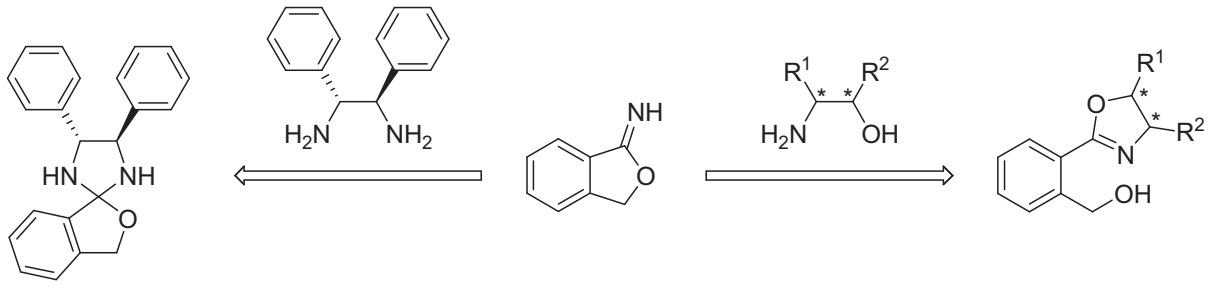
Schema 7.7. *Pd-gekatalyseerde asymmetrische allylische alkylatie met een gemengd imidaat-fosfaan ligand* ***4.55b****.*

Entry	Ligand	 **4.98**	 **4.99**	 **4.100**	Referentie
1	 **4.55b**	99% rendement 99% ee	76% rendement 74% ee	91% rendement 83% ee	5
2		28% rendement 91% ee	94% rendement 91% ee	-	6
3[a]		100% omzetting 96% ee	- 81% ee	- 82% ee	7
4[a]		100% omzetting 92% ee	100% omzetting 75% ee	- 81% ee	8
5[a]		100% omzetting >99% ee	100% omzetting 91% ee	100% omzetting 73% ee	9

[a] 

Tabel 7.1. *Vergelijking van het gemengd imidaat-fosfaan ligand (**4.55b**) met de beste resultaten uit de literatuur.*

Het cyclisch imidaat ligand precursor kon ook efficient gebruikt worden als een bouwsteen voor de synthese van chirale oxazoline alcohol liganden en de synthese van chirale imidazolidines (Schema 7.8). De chirale oxazoline alcohol liganden werden getest in asymmetrische diethylzink additions aan benzaldehydes.[10] Enantioselectiviteiten tot 87% ee werden behaald.



Schema 7.8. *Synthetische toepassingen van cyclische imidaat esters.*

We hebben in dit doctoraat aangetoond dat zowel chirale dieen liganden als chirale imidaat liganden zeer interessante liganden kunnen zijn voor asymmetrische katalyse.
Zowel wij als andere groepen hebben aangetoond dat chirale dieen liganden meer zijn dan enkel een principsbewijs. Sinds 2003 is een indrukwekkend aantal publicaties verschenen die hun uitzonderlijke katalytische eigenschappen aantonen.[11] Het is echter opmerkelijk dat bijna alle voorbeelden rhodium- en iridium-gekatalyseerde asymmetrische reacties betreffen. Het zou bijgevolgd interessant zijn om verder onderzoek te wijten aan de zoektocht naar nieuwe metalen die compatibel zijn met deze dieen liganden. Dit zou de bruikbaarheid van deze dieen ligand familie aanzienlijk verruimen.
Ondanks het feit dat het gebruik van chirale imidaat liganden tot voor kort onbestaande was, hebben wij in dit doctoraat aangetoond dat zij zeer interessant kunnen zijn in de toekomst. De eenvoudige synthese van dit ligandtype is opmerkelijk. Dit kenmerk kan het gebruik van imidaten als liganden in de toekomst sterk versnellen. In de toekomst zou het interessant zijn om nieuwe applicaties voor deze imidaat liganden te ontwikkelen. Zeker de gemengde imidaat-fosfaan liganden hebben heel wat potentieel en zouden in de toekomst verder gevaloriseerd moeten worden in verschillende testreacties.
Daarnaast toonden we aan dat het mogelijk is om de katalytische eigenschappen van het imidaat ligand aan te passen door substituenten te plaatsen op de aromatische ring van het imidaat ligand precursor. Dit aspect is uiterst belangrijk aangezien het de mogelijkheid biedt om de imidaat katalysator verder te optimaliseren voor een specifieke applicatie.

REFERENTIES

[1] Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.

[2] Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961-12967.

[3] Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E.M. *Org. Lett.* **2004**, *6*, 3873-3876.

[4] Noël, T.; Vandyck, K.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Tetrahedron* **2009**, *65*, 8879-8884.

[5] Noël, T.; Bert, K.; Van der Eycken, E.; Van der Eycken, J. **2009** (submitted for publication).

[6] Evans, D.A.; Campos, K.R.; Tedrow, J.S.; Michael, F.E.; Gagné, M.R. *J. Org. Chem.* **1999**, *64*, 2994-2995.

[7] Pàmies, O.; Diéguez, M.; Claver, C. *Adv. Synth. Catal.* **2007**, *349*, 836-840.

[8] Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943-1947.

[9] Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646-3647.

[10] Noël, T.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E.; Van der Eycken, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1962-1968.

[11] For a review about chiral diene ligands: (a) Defieber, C.; Grützmacher, H.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4482-4502. (b) Johnson, J.B.; Rovis, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 840-871. (c) Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3364-3366.